IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

HERON THERAPEUTICS, INC.,

Plaintiff,

v.

FRESENIUS KABI USA, LLC,

Defendant.

C.A. No. 22-985-WCB

[redacted]

CORRECTED VERSION: 8/6/2024
REDACTIONS APPLIED: 8/6/2024

DEFENDANT FRESENIUS KABI USA, LLC'S OPENING POST-TRIAL BRIEF

Of Counsel:

Imron T. Aly
Kevin M. Nelson
Helen H. Ji
Julie A. Vernon
ARENTFOX SCHIFF LLP
233 South Wacker Drive
Suite 7100
Chicago, IL 60606
(312) 258-5500
imron.aly@afslaw.com
kevin.nelson@afslaw.com
helen.ji@afslaw.com
julie.vernon@afslaw.com

Neal C. Belgam (No. 2721)
Daniel A. Taylor (No. 6934)
SMITH, KATZENSTEIN & JENKINS, LLP
1000 West Street, Suite 1501
Wilmington, DE 19801
(302) 504-8400
nbelgam@skjlaw.com
dtaylor@skjlaw.com

Attorneys for Defendant
Fresenius Kabi USA, LLC

Date: July 30, 2024

TABLE OF CONTENTS
(Continued)

Page

TABLE OF CONTENTS
(Continued)

Page

TABLE OF CONTENTS
(Continued)

Page

TABLE OF AUTHORITIES

Page(s)

Cases

TABLE OF AUTHORITIES
(Continued)

Page(s)

TABLE OF AUTHORITIES
(Continued)

Page(s)

TABLE OF ABBREVIATIONS

ABBREVIATION	FULL DESCRIPTION	EXHIBIT NO.
'229 patent	U.S. Patent No. 9,561,229	JTX1
'794 patent	U.S. Patent No. 9,974,794	JTX7
ANDA	Abbreviated New Drug Application	
Asserted Claims	Claims 9, 10, and 21 of the '229 patent and claims 9 and 10 of the '794 patent	
Burns	Derek Burns et al., *Best Practice Approach to Successful Conversion of Fosaprepitant to Aprepitant IV in a Large Multisite Community Oncology Infusion Center: A Retrospective Analysis*, 37 ADVANCES IN THERAPY 3265 (2020)	JTX155
CINV	chemotherapy induced nausea and vomiting	
CN845	Chinese Patent Application Publication No. CN102379845A, titled "Aprepitant microemulsion for injection and preparation method thereof," filed on November 3, 2011	JTX71
Dranitsaris	George Dranitsaris et al., *A Real-World Study to Evaluate the Safety and Efficacy of Three Injectable Neurokinin-1 Receptor Antagonist Formulations for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Cancer Patients*, 30 SUPPORTIVE CARE IN CANCER 6649 (2022)	JTX127
Emend IV	Emend for Injection	
FDA	United States Food and Drug Administration	
Fell	Gillian L. Fell et al., Intravenous Lipid Emulsions in Parenteral Nutrition, 6 ADV. NUTR. 600 (2015)	JTX76
Fresenius's ANDA Product	The drug product that is the subject of Abbreviated New Drug Application No. 214639	
Fresenius Kabi	Fresenius Kabi USA, LLC	
Hargreaves	Richard Hargreaves et al., *Development of Aprepitant, the First Neurokinin-1 Receptor Antagonist for the Prevention of Chemotherapy-Induced Nausea and Vomiting*, 1222 ANNALS N.Y. ACAD. SCI. 40 (2011)	JTX82
Hegerova	Livia T. Hegerova et al., *An Analysis of Fosaprepitant-Induced Venous Toxicity in Patients Receiving Highly Emetogenic Chemotherapy*, 23 SUPPORT CARE CANCER 55 (2015)	JTX134
Heron	Heron Therapeutics, Inc.	
Hingorani	U.S. Patent Appl. Pub. No. 2013/0317016 A1	JTX21
IV	Intravenous	

ABBREVIATION	FULL DESCRIPTION	EXHIBIT NO.
Jumaa	Muhannad Jumaa & Bernd W. Müller, *Lipid Emulsions as a Novel System to Reduce the Hemolytic Activity of Lytic Agents: Mechanism of the Protective Effect*, 9 EUR. J. PHARMACEUTICAL SCIS. 285 (2000)	JTX88
Kamat	Madhav Kamat & Patrick P. DeLuca, *Formulation Development of Small and Large Volume Injections*, in PHARMACEUTICAL DOSAGE FORMS: PARENTERAL MEDICATIONS (Sandeep Nema & John D. Ludwig eds., 3d ed., 2010)	JTX92
Karavas	International Patent Appl. Pub. No. WO 2014/005606 A1	JTX90
Khan	Barket Ali Khan et al., *Basics of Pharmaceutical Emulsions: A Review*, 5 AFRICAN J. PHARMACY & PHARMACOLOGY 2715 (2011)	JTX91
Leal	A.D. Leal et al., *Fosaprepitant-Induced Phlebitis: A Focus on Patients Receiving Doxorubicin/Cyclophosphamide Therapy*, 22 *Support Care Cancer* 1313 (2014)	JTX137
Liu	Jie Liu et al., *Progress in Research of Injectable Microemulsion*, 42 CHINESE J. PHARMACEUTICALS 300 (2011)	JTX93
Navari	Rudolph M. Navari et al., *Evolving Role of Neurokinin I -Receptor Antagonists for Chemotherapy-Induced Nausea and Vomiting*, 11 ONCOTARGETS & THERAPY 6459 (2018)	JTX139
NDA	New Drug Application	
NK-1	Neurokinin-1	
Patents-in-Suit	The '229 patent and the '794 patent	
PFAT5	Percentage of fat globules greater than 5 microns	
POSA	person of ordinary skill in the art	
[page]:[line]	format for trial transcript citations	
Strickley	Robert G. Strickley, *Solubilizing Excipients in Oral and Injectable Formulations*, 21 PHARMACEUTICAL RES. 201 (2004)	JTX105
USP	United States Pharmacopeia	
USP 1	United States Pharmacopeia, Chapter 1 (2014)	JTX107
USP 729	United States Pharmacopeia, Chapter 729 (2014)	JTX120
USPTO	United States Patent and Trademark Office	
Wan	U.S. Patent Appl. Pub. No. 2011/0038925 A1	JTX112

ABBREVIATION	FULL DESCRIPTION	EXHIBIT NO.
Washington	C. Washington, *Stability of Lipid Emulsions for Drug Delivery*, 20 ADVANCED DRUG DELIVERY REVS. 131 (1996)	JTX113
Weinstein	C. Weinstein et al., Single-Dose Fosaprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated with Moderately Emetogenic Chemotherapy: Results of a Randomized, Double-Blind Phase III Trial, 27 ANNALS ONCOLOGY 172 (2016)	DTX74
Zhou or the Zhou article	Wei Zhou et al., *Preparation of Aprepitant Emulsion for Intravenous Injection*, 43 CHINESE J. PHARMACEUTICALS 1003 (2012)	JTX116

I. Introduction

Heron took credit for the invention that CN845 already made. By the September 2014 priority date, CN845 (published in 2012) disclosed varying excipients and amounts to make aprepitant emulsions, and taught a POSA how to make these injectable formulations. There is one difference between the prior art and the Asserted Claims, albeit an obvious one: the Asserted Claims all recite 14% of the emulsifier egg yolk lecithin, whereas CN845 disclosed up to 10% of the emulsifier egg yolk lecithin. Heron's expert Dr. Steven Little, however, admitted that Heron showed no criticality for any claim term, including the claimed 14% egg yolk lecithin.

Fresenius Kabi's formulation expert Dr. Barrett Rabinow provided detailed and unrebutted testimony that increasing the emulsifier level above 10% to include 14% would have been obvious for several reasons. *First*, a POSA would have understood from CN845 that aprepitant—a drug insoluble in oil or water—can be dissolved at the interface between those two phases in an emulsion, and that using more emulsifier would increase the available interface to help drug stability. *Second*, the prior art showed up to 30% emulsifier had already been used. *Third*, a POSA would have known that phospholipids (e.g., egg yolk lecithin) can form complexes with drugs; therefore, adding more egg yolk lecithin would help to create more complexes and further stabilize the drug. A POSA would have applied routine optimization to increase emulsifier levels to establish USP stability; that is the essence of pharmaceutical formulation optimization.

Heron advanced several secondary considerations, but none were supported, either legally or factually. Heron asserted unexpected results, but Dr. Little admitted there was no "evidence of what the skilled artisan would have expected" before the alleged invention; thus, as a matter of law there could be no "unexpected" result that the claimed formulations were stable. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). Moreover, Heron never provided an apples-to-apples comparison that could permit one to conclude that the emulsifier level itself improved

stability. For long-felt, unmet need, Heron relied on physician Dr. Eric Roeland to assert an alleged need for a formulation with less adverse reactions than Emend IV; however, he never showed prior art publications expressed a need to reduce any adverse reactions. On the other hand, Fresenius Kabi's expert Dr. Maurie Markman showed that doctors knew how to mitigate or eliminate any adverse reactions. For "failure of others," Dr. Little assumed "failure" because the CN845 and Zhou products were not commercialized; however, non-commercialization does equate to a "failure." In any event, Heron offered no evidence that anyone tried to commercialize a product of CN845 or Zhou, much less tried and failed; and those references both showed successful examples of emulsions. Heron also alleged "copying," but Dr. Little admitted that Fresenius Kabi used the same formulation as Heron's formulation for regulatory (not technical) reasons. Finally, Heron's economist Mr. Michael Tate testified about commercial success; however, Fresenius Kabi's expert Mr. Anthony Masztak showed that Cinvanti sales were a result of strategic pricing and contract terms not, as Heron claims, a lack of polysorbate 80 or the "2-minute push" option.

Finally, to show infringement for claims 9 and 10 of the '794 patent, Dr. Little relied on inherency, asserting that products with the same formulation as Cinvanti would necessarily meet the "physically stable" claim term, including the microscopy requirement. Heron cannot have it both ways: either the physical stability property is inherent for all such compositions or Heron's lack of evidence falls short of establishing infringement. For written description, all Asserted Claims require the pH range of 7.5 to 9.0; however, the only working examples in the Patents-in-Suit used a pH within the narrow range 8.74 to 8.92. The patent specification even distinguished examples that used "pH of less than 8.0," underscoring the lack of possession of the full pH range, particularly for the pH portion 7.5 to 8.0.

Thus, judgment should be entered in favor of Fresenius Kabi.

II. State of the Art as of the September 2014 Priority Date

The state of the prior art had significantly evolved by the priority date. Aprepitant was an old drug, but prior art published in 2012—notably CN845 and Zhou—showed how to use emulsions to make aprepitant intravenous formulations. That turning point showed why and how to formulate intravenous aprepitant, and highlights why Heron's "hindsight" argument is baseless.

A. The Role of NK-1 Receptor Antagonists

Certain cancer drugs often cause CINV. 142:17-24 (Rabinow); JTX71.11; 568:14-569:5 (Markman). The NK-1 receptor is a receptor in the brain that affects the body's nausea and vomiting reflex, to help reject foreign substances. 141:23-142:12 (Rabinow); JTX71.11; 571:3-573:8 (Markman). NK-1 receptor antagonists are drugs that fit within the NK-1 receptor, temporarily impeding the emesis response while chemotherapy is administered. 141:23-142:12 (Rabinow); JTX71.11; 573:3-573:8, 573:12-20 (Markman). NK-1 receptor antagonists offered an important complement to other existing anti-CINV drugs, because they work on a different receptor system and offer relief from delayed nausea and vomiting. 583:21-585:5 (Markman).

B. Development of Aprepitant and Fosaprepitant

Merck worked in the early 1990s to develop a new NK-1 receptor antagonist compound. JTX82.2. Merck's work involved synthesizing various chemical compounds and testing them for activity against the NK-1 receptor. *Id.* at 3. That work resulted in the NK-1 receptor antagonist aprepitant. *Id.* at 3-4. More specifically, in 1993, Merck developed the compound aprepitant, and over the years showed its safety and efficacy in treating CINV. *Id.* at 7. In 2003, Emend (aprepitant), an oral formulation, became the first NK-1 receptor antagonist approved by FDA; aprepitant "was an incredibly important advance" in treating CINV when administered with other anti-emetics. 583:21-585:5 (Markman); JTX82.3, .5-.7; *see also* 913:4-13 (Hale).

The physiochemical properties of aprepitant were well known prior to 2014. In particular,

aprepitant was known to be poorly soluble in oil or water. Dating back to the 1990s, Merck developed the compound fosaprepitant, a prodrug of aprepitant that was water-soluble, and converted to the active aprepitant molecule once in the body. JTX82.7; *see also* JTX82.5; 122:11-15 (Rabinow). The prodrug approach chemically modified aprepitant by adding a cleavable phosphate group that helped the drug dissolve in water, and cleaved to reveal the active aprepitant compound once administered to a patient. JTX82.5; 122:11-15 (Rabinow). So when a patient is administered fosaprepitant, a POSA understood that aprepitant was providing the biological response in the patient. 586:7-10 (Markman); 1017:4-8 (Roeland). Injectable fosaprepitant was first FDA-approved in 2008, and known as Emend IV. JTX82.7; 124:24-125:8 (Rabinow).

As of September 2014, there was no doubt that "aprepitant was known to be efficacious for treating CINV." 1081:5-9 (Roeland). In 2014, Emend and Emend IV were the only FDA-approved NK-1 receptor antagonists. 977:3-10 (Hale). The Emend IV formulation used polysorbate 80, which was reputed to cause hypersensitivity reactions. 122:18-123:7 (Rabinow). There remained a desire to develop an injectable aprepitant formulation that (i) used aprepitant itself rather than the costly and complicated fosaprepitant prodrug, and (ii) did not use polysorbate 80. 125:17-126:5, 143:19-144:3 (Rabinow).

C. Status of Other NK-1 Receptor Antagonists

Because aprepitant and fosaprepitant were the only FDA-approved NK-1 receptor antagonists, a POSA would have focused on those drugs for formulation development since aprepitant's efficacy had been established. 126:6-17, 128:7-129:11 (Rabinow); DTX47.22 (Table 1). Other NK-1 receptor antagonist candidates were still in development as of 2014, and two (rolapitant and netupitant) were undergoing Phase III clinical trials with the hope of someday obtaining FDA approval. 944:17-945:11 (Hale); DTX47.22 (Table 1). Those drugs, however, were newly patented, making it less likely someone else would want to reformulate them. 943:2-

945:11 (Hale). Moreover, rolapitant and netupitant were already formulated as injectables, without the use or need for prodrugs, and without any published concerns or stated objectives for improvement. 944:17-945:11 (Hale). Therefore, by 2014, when more information became available about formulating aprepitant, a POSA would have been motivated to pursue an injectable aprepitant presentation. *See* 125:17-22, 280:24-282:20 (Rabinow).

D. 2012 Publications Taught Aprepitant Emulsion Formulations

Detailed formulation information specifically for aprepitant became available in 2012, when CN845 and Zhou both published. *See* 130:23-131:5 (Rabinow). These references taught how to formulate injectable aprepitant formulations using emulsions. 133:11-15, 189:21-190:17 (Rabinow); *see generally* JTX71; JTX115. CN845 was the first known publication to have disclosed and tested emulsions using aprepitant. 131:22-24, 132:21-133:15 (Rabinow); 1376:18-1377:2 (Little). CN845 listed ranges of excipients commonly used in emulsions, and tested eight example formulations that all resulted in aprepitant emulsion formulations. JTX71.13-17; 133:16-24, 157:15-161:2, 164:23-166:15 (Rabinow). CN845 expressly confirmed problems with existing approaches that the new emulsion solved: oral aprepitant was not ideal for patients at risk for nausea and vomiting, and making fosaprepitant required expensive and complex chemical synthesis. JTX71.12; 143:10-18, 280:24-282:20 (Rabinow). Thus, CN845 provided express teaching, suggestion, and motivation to support obviousness, even though *KSR* made clear that the express test was not required. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419 (2007). Zhou used a particular aprepitant concentration (0.25 wt/wt%) and then tested formulations optimized for a particular purpose, i.e., a stability variable called K_e, a centrifugation constant that provided helpful stability information. 192:15-193:6, 196:9-197:1 (Rabinow); JTX115.7.

As of 2012, therefore, CN845 and Zhou demonstrated to the POSA that the emulsion approach should be used with aprepitant. 166:25-167:5, 190:15-17 (Rabinow). A POSA would

have recognized why emulsions solve the aprepitant formulation solubility problem. As Washington taught, if a drug was not soluble in oil or water but was soluble in an emulsion, then the drug could reside at the ***interface*** between the oil and water phases. 170:22-172:14, 173:19-174:12 (Rabinow); JTX113.9.

In order to commercialize the prior art teaching, a POSA would have known the formulation would need to meet USP standards, and in particular the USP 1 and USP 729 stability requirements for injectable formulations. 167:6-15, 209:12-212:20, 213:6-214:9 (Rabinow); JTX107; JTX120; *see also* 468:10-469:3 (Han); 521:16-522:12 (Ottoboni).

III. Level of Ordinary Skill

Dr. Rabinow proposed the following POSA definition upon which Fresenius Kabi's experts relied in forming their opinions: "a POSA relevant to the patents-in-suit is an individual with an advanced degree in pharmaceutical formulation, pharmaceutical chemistry, medicinal chemistry or a related field and experience with intravenous emulsion formulations. Such a person would also consult with or have access to a medical doctor specializing in oncology or a general practitioner having 2-3 years of experience treating patients with cancer." 129:19-130:6 (Rabinow). Heron's proposed POSA definition is substantially similar but uses: (1) a lower requirement for education such as a bachelor's degree in pharmaceutics (131:7-14 (Rabinow); 1212:24-1213:2 (Little)) and (2) a broader experience in "parenteral drug products or injectable drug products" as opposed to emulsion formulations, 1213:15-1214:1 (Little). Given the substantial overlap, experts from both sides agreed and confirmed that their opinions would not change under either POSA definition. 130:15-17 (Rabinow); 1214:6-14 (Little).

IV. The Asserted Claims Would Have Been Obvious to a POSA

The state of the art by the September 2014 priority date rendered obvious the claimed emulsion formulations. As discussed herein, aprepitant was known to have low solubility in oil or

water. Exploiting that very same property, CN845 and Zhou made emulsion formulations, and thereby was successfully able to make an IV NK-1 formulation using aprepitant in particular. Aprepitant was an FDA-approved drug, with a history of efficacy, and with room for improvement in an IV formulation that avoided polysorbate 80, and avoided the costly and complex fosaprepitant prodrug. CN845 and Zhou solved these problems.

A. Scope and Content of the Relevant Prior Art

CN845 identified the problem with prior art aprepitant formulations, used emulsions to solve the problems, and tested several examples using different amounts and types of common emulsion ingredients. JTX71.12-17; 143:10-18, 164:23-165:1, 166:11-15, 280:24-282:20 (Rabinow); 1374:8-15 (Little). While most drugs do not require the emulsion approach (266:8-267:8, 267:19-21, 270:17-271:12 (Rabinow); 1275:1-1278:1 (Little)), aprepitant had unique properties that lended itself to that approach, 121:3-10, 164:23-165:1 (Rabinow); 1320:25-1321:13, 1373:8-16 (Little). Dr. Rabinow considered Strickley and Kamat, references that described formulation approaches when considering any drug generally; he explained why by 2014 the emulsion approach was appropriate for aprepitant specifically. 273:15-19 (Rabinow (discussing JTX105.25-26)); 277:4-21 (Rabinow (discussing JTX92.33-34)). As both formulation experts agreed, the emulsion approach has its place, and CN845 confirmed that aprepitant was suitable for emulsions. 272:12-273:14 (Rabinow); 1280:3-14 (Little).

CN845 disclosed emulsions using aprepitant, excipients, and ranges for those excipients. JTX71.13-17; 133:16-24, 164:23-165:1, 166:11-15 (Rabinow); 1217:16-1218:8, 1373:8-16 (Little). CN845 taught aprepitant emulsions containing 0.05-2.0 wt/wt% aprepitant. JTX71.13, [0008]. CN845 also taught that the preferred oil was soybean oil and the preferred emulsifier was egg yolk lecithin. 144:22-145:7, 146:6-13 (Rabinow); JTX71.13 [0010]. It was common for POSAs to pair these two excipients for emulsions. 146:14-25 (Rabinow). Egg yolk lecithin was

known as a naturally occurring phospholipid, and known to contain constituent parts that include oleic acid. 159:15-160:5 (Rabinow); 1249:20-1250:9, 1415:23-1416:12 (Little). CN845 disclosed and tested emulsifier levels up to 10 wt/wt%, and emulsifier-to-drug ratios of up to 49:1. JTX71.13, .17; 242:14-244:23, 245:5-15, 245:18-21 (Rabinow); 1220:2-1222:1 (Little).

CN845 included eight Examples, with different excipients within each category and with different amounts of excipients. JTX7.14-17; *see also* 164:23-165:1, 166:4-10 (Rabinow); 1220:2-1222:1 (Little). As Dr. Little explained on direct and reconfirmed on cross, CN845's Examples spanned the ranges that CN845 itself disclosed. 1220:2-1222:1, 1374:16-1375:15 (Little). All Examples resulted in emulsions. 166:11-15 (Rabinow); 1373:8-16 (Little). CN845 also disclosed a pH window of 6.0-8.0, and the eight Examples all used a pH between 6.8 and 8.0, consistent with a POSA's knowledge that pH levels at around 7.0 or above would be preferred. JTX7.13-17; *see also* 163:23-164:20 (Rabinow). CN845 remains the earliest known publication of an aprepitant emulsion, and it demonstrated how and why to make an aprepitant emulsion. 133:11-15, 166:25-167:5, 282:10-20 (Rabinow); 1373:8-16 (Little).

A POSA would have known of established stability criteria for intravenous products, especially the USP requirements. 167:6-15, 209:12-17, 211:20-212:7 (Rabinow); *see also* 468:10-469:3 (Han); 521:16-522:12 (Ottoboni). CN845 did not contain stability testing data, but as the experts agreed, its focus was to show aprepitant emulsions were made. 133:11-15, 144:4-12 (Rabinow); 1373:8-16 (Little). CN845 still provided information to show stability, because it "autoclaved for 30 minutes at 115°C" some of its samples and retained emulsions. JTX71.16-17.

Further, by September 2014, Zhou carried out a proof-of-concept demonstration for an aprepitant emulsion formulation, with stability data. 190:22-191:1, 192:15-193:6 (Rabinow); 1253:6-9 (Little). Zhou picked a fixed aprepitant and oil concentration, and then evaluated four

variables, optimizing them based on the centrifugation constant "K_e." JTX115.7; 192:19-193:6, 196:12-197:1 (Rabinow); 1254:25-1255:25 (Little). The K_e constant provided information for physical stability over time (1397:12-15 (Little)) and demonstrated that an aprepitant emulsion can be stable according to that variable, (204:7-13 (Rabinow)). While K_e is useful, it is not the same as the USP requirements for visible crystals and PFAT5. 209:4-11 (Rabinow); 1393:25-1394:7 (Little). Among other results, Zhou expressly provided particle size results after three months at both room temperature and refrigerated conditions, again showing stability over time. JTX115.8 (Table 2), 10 (Table 4); 202:24-203:9, 204:7-13, 205:23-206:3 (Rabinow); 1394:18-1395:8 (Little). Dr. Little agreed that Zhou's particle size tests met USP. 1394:22-1395:12 (Little).

Once CN845 published, a POSA would have understood why and how an emulsion solution to the aprepitant formulation worked. A POSA also knew that drugs that are not soluble in oil or water, labeled "Class III" drugs by Washington, can accumulate at the interface between the oil and water phases of an emulsion. JTX113.9; 171:23-172:14, 173:19-174:12 (Rabinow); 1379:17-1381:2 (Little). A POSA already knew that emulsions formed by stabilizing oil and water phases using an emulsifier, a molecule with both lipophilic and hydrophilic portions that can bridge the two phases, serving as a "diplomat" between the two. 134:19-135:12 (Rabinow). In fact, a POSA would have appreciated that aprepitant itself has lipophilic and hydrophilic components independently compatible with the interface, to interact with both the oil and water phases. 172:2-14 (Rabinow); 1377:3-20 (Little). A POSA further understood that increasing emulsifier levels would both make oil globule sizes smaller and increase interface surface area, providing more places for more drug to remain stable over time. 136:10-137:11, 175:24-176:14 (Rabinow); 1425:14-1426:13 (Little).

B. The Prior Art Expressly Motivated a POSA to Develop an IV Formulation of Aprepitant

In view of the prior art, the POSA would have sought to make aprepitant IV formulations rather than reformulating other drugs. 279:15-280:2 (Rabinow). "[O]bviousness 'does not require that the motivation be the best option, only that it be a suitable option from which the prior art did not teach away.'" *Bayer Pharma AG v. Watson Labs, Inc.*, 874 F.3d 1316, 1328 (Fed. Cir. 2017) (citing *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1197-98 (Fed. Cir. 2014)). By 2014, aprepitant was the *most* suitable option, at least because aprepitant was FDA-approved and in formulations that both parties' experts agreed invited improvements that the prior art already addressed. JTX71.11 ("Aprepitant is the only one already marketed NK-1 receptor drug.")

As of 2014, the aprepitant compound was known as "an incredibly important advance" in the treatment of CINV, as physicians quickly adopted the oral product because of its benefits in addressing nausea and vomiting, and in particular delayed-onset CINV. 583:21-585:5; 587:22-588:21 (Markman); JTX82.2. So there was no doubt that "aprepitant was known to be efficacious for treating CINV before 2014." 1081:5-9 (Roeland).

As both Dr. Rabinow and Dr. Markman testified, a POSA would prefer IV aprepitant over oral aprepitant. It was known by 2014 that oral drugs are harder to give to a patient suffering from nausea and vomiting who may not be able to ingest such medications, and would have compliance issues. 121:18-122:1 (Rabinow); 577:21-580:14 (Markman); *see also* 1020:8-1021:7 (Roeland). Intravenous formulations, in contrast, provide immediate and confirmed therapy. 143:5-18 (Rabinow); 577:21-580:14 (Markman); 1017:12-1018:7 (Roeland). The known efficacy of aprepitant, with the known benefits of an IV formulation, would have motivated a POSA to make an intravenous aprepitant product. 577:21-580:14, 590:8-591:14, 593:5-594:19, 596:4-11 (Markman); JTX82.5, 7; JTX71.12 at [0006], 14 at [0015].

Fosaprepitant was available in an IV formulation, but it used the aprepitant prodrug.

CN845 expressly explained some known downsides of using fosaprepitant, including the extra cost and more complex synthesis compared to aprepitant itself. JTX71.12 at [0006]. CN845 expressly reported that "compared with a fosaprepitant dimethyl-meglumine injection, the aprepitant microemulsion has the advantages that: the cost is reduced greatly, the practicality is extremely high, and economic and social benefits are relatively good." JTX71.1. Even Dr. Hale admitted IV aprepitant is preferable over IV fosaprepitant because it is "conceptually simpler" to avoid a prodrug. 930:16-931:8 (Hale).

Fosaprepitant's formulation also contained polysorbate 80, which Heron asserts caused allergic reactions (1035:6-19 (Roeland)); a POSA concerned about possible allergic reactions would have been motivated to develop aprepitant formulations that did not use polysorbate 80 (1428:25-1429:11 (Little)).

In 2012, CN845 disclosed factors that would have motivated a POSA to develop an IV aprepitant formulation, explaining that "***[a]prepitant*** injectable dosage forms are of great significance for the clinical treatment." JTX71.12 at [0006] (emphasis added). CN845 pointed to aprepitant's already-established efficacy as an NK-1 receptor antagonist, its previously-approved availability as an oral formulation, and benefits over the fosaprepitant prodrug. *Id.*; *see also* JTX71.11 at [0002]. Other publications in the same time frame confirmed this interest in intravenous aprepitant, including emulsions. In 2013, Hingorani reported "aprepitant is substantially insoluble in both oil and water" and "various emulsion formulations could be prepared from which aprepitant did not precipitate." JTX21.7 at [0054]; *see also* 259:23-261:12 (Rabinow). In 2014, Karavas reported making an "intramuscular (IM) or subcutaneous (SC), formulation of Aprepitant or Fosaprepitant," including the approach of "emulsions (aqueous and non-aqueous)." JTX90.5 at ll. 18-27; *see also* 264:14-266:1 (Rabinow).

Dr. Hale shared his experience from a medicinal chemist's point of view—not a formulator's or POSA's—synthesizing chemical compounds at Merck in the 1990s. Dr. Hale's experience and testimony are irrelevant. Dr. Little in fact conceded that he had no knowledge of Merck's formulation efforts and saw no publications about them. 1399:19-1400:4 (Little).

Heron has referenced *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853 (Fed. Cir. 2015), to argue that the obviousness analysis requires ruling out all NK-1 receptor antagonists before considering aprepitant. That is an incorrect reading of *Insite*, and in any event that case is inapplicable here. *Insite* supports Fresenius Kabi's position because it focused on what the prior art actually disclosed for the drug at issue. *See Insite*, 783 F.3d at 860. The patent at issue in *Insite* was not directed to "specific formulations" but instead at "look[ing] at the feasibility" of a new medical use. *InSite Vision Inc. v. Sandoz Inc.*, C.A. No. 11-3080, 2013 WL 5975015, at *14 (D.N.J. Oct. 4, 2013). Specifically, in *Insite*, the drug azithromycin had previously been orally administered to treat infections inside the body (like sinus infections), but had not been considered for the claimed topical administration of treating eye infections, and the prior art actually discouraged such use because the drug's therapeutic characteristics made it "a poor choice for treating ocular infections." *Insite*, 783 F.3d at 860. In sharp contrast, the prior art in this case expressly taught injectable formulations using aprepitant in particular, and for the same nausea and vomiting use that was already established in the prior art. *See, e.g.*, JTX71; JTX21; JTX91. CN845 expressly declared its focus on IV aprepitant formulations. (JTX71.12, ¶ 0006). Thus, there was no difference in what the Patents-in-Suit set out to do and what the prior art already did: use aprepitant emulsions to make injectable intravenous formulations.

The evidence here meets even Heron's improper legal standard, which would require Fresenius Kabi to first show why a POSA would consider reformulating aprepitant, and only then

proceed to show why the aprepitant prior art rendered obvious the claimed invention. Such a "lead compound"-type analysis only applies in cases involving modifications to chemical compounds and is legally irrelevant in formulation cases like this one. *See Bayer*, 874 F.3d at 1328-29 (overturning district court's finding of no motivation to create a particular formulation). In formulation cases, "[a]ny motivation, 'whether articulated in the references themselves or supported by evidence of the knowledge of a skilled artisan, is sufficient.'" *Id.* at 1324 (quoting *Outdry Techs. Corp. v. Geox S.p.A.*, 859 F.3d 1364, 1370-71 (Fed Cir. 2017)). In *Bayer*, the Federal Circuit held "the motivation to formulate an ODT version of vardenafil is plainly evident from the face of multiple prior art references disclosing ODT formulations of ED drugs. ***No further rationale for developing vardenafil ODT was necessary***." *Id.* (emphasis added). Here, the motivation to create an IV formulation of aprepitant is even more expressly supported by the prior art, which identified the need for intravenous aprepitant specifically in references published in 2012-2014 leading up to the priority date. *See, e.g.*, JTX71.12 at [0006]; JTX115.5; JTX21.2 at [0009]; JTX90.3 at ll. 24-28.

Thus, even using the improper legal standard Heron attempts to impose here, where aprepitant had to be first identified as a candidate for reformulation and then reformulated, Fresenius Kabi has still met that burden here. Dr. Rabinow assessed the NK-1 landscape as of the priority date and showed why a POSA would have improved aprepitant formulations, especially given the express teachings about aprepitant in particular. 125:17-22, 126:6-17, 128:7-129:11 (Rabinow). In other words, the prior art already made the choice and identified aprepitant as the NK-1 receptor antagonist to pursue as an intravenous formulation. 279:11-280:2 (Rabinow).

C. A POSA Would Have Been Motivated to Combine the Prior Art, Namely CN845 and Zhou, in View of Washington, Liu, and/or the Knowledge of a POSA to Obtain an IV Formulation of Aprepitant

With CN845 providing the solution to the aprepitant IV formulation issue, a POSA looking

to make an intravenous formulation of aprepitant would have been motivated to take CN845's teachings and optimize emulsion formulations according to USP 1 and USP 729. 226:14-227:3 (Rabinow). To do so, the POSA would have had prior art teachings, along with experience and knowledge, to work with CN845 and focus on increasing emulsifier levels. A POSA would have thus combined CN845 and Zhou, along with Washington, Liu, and/or the POSA's knowledge.

CN845 "transformed" the state of the art in 2012, because it detailed how to formulate aprepitant in an injectable solution. 132:21-133:15 (Rabinow). CN845 contained the classic components of an emulsion: oil, emulsifier, co-emulsifier, and protectant. JTX71.13; 134:6-18 (Rabinow). CN845 used a significantly higher amount of emulsifier for its aprepitant formulations, as compared to amounts used in standard emulsions. A POSA would have understood "exactly what is happening, what the result is, and why" in CN845. 170:22-171:3 (Rabinow); JTX113.9. Washington explained that Class III drugs (e.g., aprepitant) can be loaded into an emulsion by "adsorbing to the droplet interface": i.e. the "interface" between the oil and water phases of an emulsion. 171:16-172:14 (Rabinow); JTX113.9. Thus, the POSA would have recognized that increasing the available interface region would improve aprepitant stability. 173:19-174:15 (Rabinow) ("So if you want to have a good chance of loading the drug onto the interface, you've got to have a large interface."). "CN845 said, Look, here is a drug, aprepitant, that is insoluble in both water and oil, and we're going to formulate it as an emulsion. That was not really done before." 133:11-15 (Rabinow).

Zhou's lead author, Wei Zhou, was the first named inventor on CN845. Zhou added physical stability testing and oleic acid, along with a 10:1 ratio of emulsifier to drug and a 7.3 pH—all to show as a proof of concept that not only were emulsions possible, but they were stable as well. JTX115; 202:16-204:25, 323:20-324:7, 328:24-329:4 (Rabinow). Zhou also expressly

taught that egg yolk lecithin served multiple functions in an aprepitant emulsion: "Phospholipids are often used as emulsifying agents but they play the role of solubilization in this recipe." JTX115.11; *see also* 158:11-18, 217:9-218:12 (Rabinow). And while Zhou did not optimize for USP in particular, Zhou did use K_e with promising results. 192:19-193:11 (Rabinow).

The POSA would also have understood that CN845 and Zhou involved forming complexes, by combining emulsifiers—in particular phospholipids like egg yolk lecithin—and drugs. *See* 154:16-19 (Rabinow). Examples of phospholipid-drug complexes known to a POSA included bilobalide (Bombardelli, JTX74), oxymatrine (Yue, JTX114), and resveratrol (Agarwal, JTX67). 178:2-181:19 (Rabinow). A POSA would have concluded complexes formed because of the formulation process that CN845 used. CN845 first taught dissolving emulsifier and drug in ethanol, and then evaporating some of the ethanol, in order to help combine emulsifier and drug together—before adding it to the oil phase. 154:4-155:15, 181:24-182:5 (Rabinow). The first step entailed combining aprepitant and emulsifier in ethanol, and then evaporating the ethanol to form a "sticky residue," and to continue heating until a clear substance was obtained. 153:9-154:3 (Rabinow.) This process, Dr. Rabinow noted, allowed the aprepitant and emulsifier to come into contact and offered complexation opportunity. 151:6-152:17, 158:11-18 (Rabinow). To further support the POSA's conclusion that CN845 was forming complexes, CN845 also used substantially more emulsifier than had been used in the prior art for making standard emulsions—up to 10% emulsifier—and gave examples with emulsifier:drug ratios of up to 49:1. 155:19-156:15 (Rabinow); JTX71.13, .17.

Complex formation thus would have provided yet another reason to increase emulsifier levels to help stability, because a POSA would have understood that more emulsifier means more opportunity for the drug to complex with the emulsifier and remain stable in an emulsion. 177:7-

178:1 (Rabinow). Dr. Rabinow's explanation of a POSA's knowledge comports with what CN845 accomplished: aprepitant by itself is not soluble in oil, whereas after exposing aprepitant to emulsifier, the combination of the two ***was*** soluble in oil. 156:16-157:14 (Rabinow). Dr. Little offered no other explanation for why aprepitant emulsions dissolved aprepitant, and in fact agreed that one way to make complexes would be to combine drug and emulsifier in a separate step—exactly what CN845 did. 1386:23-1387:1 (Little); JTX71.14 [0016].

A POSA would have been motivated to combine CN845 and Zhou with the Liu reference (JTX93). Liu offered a POSA guidance about excipients used in emulsions, i.e., emulsifiers (a term synonymous with "surfactants"). 220:17-221:6 (Rabinow). Because CN845 and Washington taught to increase the surface area of the system to make oil droplets smaller, a POSA would have recognized that "the emulsifier level would be the most important" variable identified in CN845. 219:18-23 (Rabinow). Thus, the POSA would have been motivated to look to emulsion references to understand how much emulsifier had been used in other emulsion formulations. 226:15-227:3 (Rabinow). Liu disclosed a range of 5-30% emulsifier. JTX93.10; 223:1-8 (Rabinow). As Dr. Rabinow explained, the POSA would have recognized that Liu taught the safety of using high amounts of "phospholipids" in particular, making CN845's egg yolk lecithin (a phospholipid) eligible for the full range up to 30%. 226:16-25 (Rabinow); JTX93.11.

D. A POSA Would Have Applied Routine Optimization for Stability.

Claims that are drawn to optimized combinations of prior art ranges are invalid. This is an obviousness of ranges case, and not a genus/species case. In *Pfizer, Inc. v. Apotex, Inc.*, the Federal Circuit relied on a collection of cases to confirm the obviousness of "the optimization of a range or other variable within the claims that flows from the 'normal desire of scientists or artisans to improve upon what is generally known." 480 F.3d 1348, 1368-69 (Fed. Cir. 2007) (quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)). *In re Peterson* assessed claims with 11 variables

that overlapped with the prior art. 315 F.3d at 1329. The *Peterson* court held that "[a] prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art." *Id*. In response, a patentee can show criticality, or evidence that the specifically claimed values impart some unexpected result, but barring any such showing, claims to ranges that overlap with the prior art are invalid. *Id*. at 1330-31; *see also Galderma Laby's, LP v. Tolmar, Inc.*, 737 F.3d 731, 737-38 (Fed. Cir. 2013) (stating that, where claimed ranges overlap the prior art, "burden of production falls upon the patentee" to show teaching away, unexpected results, or some other secondary consideration)*; In re Aller*, 220 F.2d 454, 456 (Fed. Cir. 1955) (finding obviousness where, without proof of "criticality, "it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification").

Pfizer also discussed *Merck & Co., Inc. v. Biocraft Laby's., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989), which addressed the obviousness of "recited dosage limitations." There, "[t]he evidence at trial showed that, though requiring time and care, the experimentation needed to arrive at the claimed dosages was nothing more than routine." *Id*. The same is true here: the claimed excipient amounts would have required "nothing more than routine" optimization. *See Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 730 (Fed. Cir. 2017) (stating "those are all experimental details that one of ordinary skill would have utilized via routine experimentation, armed with the principles disclosed in the prior art").

It was undisputed that a POSA would have known to satisfy USP criteria in order to meet FDA approval. 208:15-22, 209:2-17 (Rabinow); 1267:1-1268:7 (Little). "USP is a recognized standard, standards in the United States for which commercialized medications must comply. And FDA expects that this is a minimum standard that all medications will comply with the appropriate sections in the USP." 208:9-14 (Rabinow). In other words, a POSA would have known to "make

sure any drug formulation he's working on will, in fact, comply with those standards" in order to allow him to pursue FDA approval of any intravenous aprepitant product in the United States. 208:8-209:22 (Rabinow). Dr. Little conceded that the USP standards provided required objectives for FDA approval and commercialization, and were so commonplace that even a scientist with a bachelor's degree would have known about them. 1267:1-1268:7, 1440:1-7 (Little). Even named inventor Dr. Ottoboni admitted that "[s]omeone developing a product would go to the Pharmacopeia very early on to understand the requirements", including for "stability" in particular. 521:16-522:12. In particular, USP 1 relates to visible crystals, and USP 729 relates to PFAT5 and particle size requirements. JTX107.8; JTX120.3; 211:7-214:4 (Rabinow). A POSA would have designed a series of tests based on the prior art ranges including eligible emulsifier ranges to optimize for stability. 214:5-215:12 (Rabinow).

Importantly, Dr. Little admitted that stability tests were indeed routine, even if they took time. 1393:7-14 (Little). The POSA's routine job would have included varying excipient levels to assess formulation stability, and the POSA's focus following the prior art in this case would have been on optimizing emulsifier level for USP stability. 223:15-224:2 (Rabinow.) Zhou already gave "an example" of "how do you do a routine optimization." 224:8-20 (Rabinow). Dr. Little similarly explained that Zhou selected and varied parameters, and then determined "optimal formulation concentrations…based on the centrifugal dissociation constant, kinetic constant [K_e]." 1254:25-1255:25. Similarly, the POSA would have been motivated "to routinely optimize the Zhou formulation so that it could be demonstrated to comply with USP." 208:23-209:11 (Rabinow).

To meet USP physical stability criteria, a POSA would have recognized that the "result-effective variable" to optimize for physical stability was the emulsifier level. *Pfizer*, 480 F.3d at

1368 (quoting *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980)). The Khan reference made this POSA knowledge explicit: "[t]he amount of emulsifying agent is one of the most important factors having an influence on the emulsion stability." JTX91.5; *see also* 168:16-169:13 (Rabinow). As discussed above, and based on the prior art teachings from CN845's own formulation protocol and Washington, a POSA would have recognized that increasing emulsifier imparts at least three benefits: increasing oil-water emulsion stability, increasing interface surface area, and decreasing globule size. 135:19-137:11, 173:19-174:15 (Rabinow). The POSA would have therefore varied emulsifier levels to meet USP requirements, using CN845 ranges and amounts above and below the ranges as part of routine optimization. 216:7-18, 218:16-219:6 (Rabinow). The rest of the emulsion components were standard fare for emulsions. 134:6-18 (Rabinow).

A POSA would have used CN845's disclosure of workable aprepitant emulsions, and varied emulsifier levels including with values "that were less than and greater than some of these levels here." 218:13-219:17 (Rabinow). Liu showed that 5-30% surfactant (which term is used interchangeably with emulsifier) was already used for making emulsions. JTX93.10; 220:5-24 (Rabinow). Dr. Rabinow testified that Liu emphasized phospholipids are safe to use and are especially eligible for the range up to 30% emulsifier that Liu reported had been used. 222:7-228:8; *see also* JTX93.10-11. Dr. Little attempted to narrow the disclosures of Liu to formulations labeled "microemulsions," (1295:10-1296:3); however, he ultimately conceded that microemulsions are a type of emulsion, that the terms overlap substantially, and that even CN845 called the disclosed aprepitant formulations "microemulsions," although a POSA would understand CN845 technically made emulsions, (1422:20-1423:23 (Little); *see also* 162:9-24 (Rabinow); JTX71.8). Others in the prior art had also acknowledged the overlapping usage of these terms. JTX110.3; 445:5-446:9 (Rabinow).

In sum, a POSA would have combined CN845 and Zhou with Washington, Liu, and/or a POSA's knowledge to optimize CN845 formulations using egg yolk lecithin ranges up to 30%.

E. A POSA Would Have Had a Reasonable Expectation of Success Based on the Prior Art and the Knowledge of a POSA

Against the backdrop that increasing emulsifier would have been reasonably expected to impart stability benefits, a POSA would have optimized within the disclosed 5-30% range, with a reasonable expectation of success. 223:1-14, 228:15-20, 251:15-25 (Rabinow).

To show a reasonable expectation of success, "only a reasonable expectation of success, not a guarantee, is needed." *Pfizer*, 480 F.3d at 1364 (citations omitted). "[C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Id*. "Indeed, a rule of law equating unpredictability to patentability" would mean that any new stable formulation "would be separately patentable" just because stability "must be verified through testing." *Id*. Put another way, absolute predictability is "not the criterion." *Merck*, 874 F.2d at 809.

In view of CN845 and Zhou, a POSA would have reasonably expected to achieve USP-stable aprepitant emulsions applying routine optimization to the prior art. 230:19-231:7 (Rabinow). CN845 already disclosed particle sizes that were 50 nm – 150 nm, which easily satisfied the 500 nm threshold from USP 729. 238:3-239:5 (Rabinow). CN845 "autoclaved for 30 minutes at 115℃" four of its eight Examples and still retained emulsions. JTX71.16 at [0028] & [0030], 17 at [0033] & [0036]. Dr. Rabinow explained that this sterilizing step "is a very severe stress for an emulsion because it tends to separate out the phases" so Zhou provided positive support for emulsion stability. 246:9-18 (Rabinow). Dr. Little similarly acknowledged that CN845's sterilization "applies a pressure" even though CN845 did not separately report physical stability test results. 1226:15-1227:7 (Little).

Zhou centered its optimization around the centrifugation constant K_e, which "incorporates both a stressor to the emulsion as well as a measurement of the result in instability." 194:13-22 (Rabinow). The K_e test is a "centrifugation test where they put the emulsion in a tube" and "spin it" with the "intent being to separate the phases." 192:19-193:6 (Rabinow). Dr. Rabinow testified that Zhou's encouraging K_e optimization result supported a reasonable expectation of success for USP, because "[t]hey found that they were able to achieve a formulation of aprepitant emulsion that was optimized for K sub E." 193:7-194:12 (Rabinow). Dr. Little conceded that Zhou taught a "stabli[zi]ng" formulation "according to the KE values." 1397:12-23 (Little). In fact, Zhou's formulation already met the particle size requirement for "physically stable" formulations, under both room temperature and refrigerated conditions. 1395:2-12 (Little). Zhou also discussed crystal formation, but did not report seeing any crystals, which a POSA would take as a promising sign. 238:3-239:5 (Rabinow). Zhou measured other criteria as well, which also remained stable over time, and supported a reasonable expectation of success to meet USP requirements. JTX115.10 (Table 4); 202:16-204:13 (Rabinow).

Washington gave further support for a reasonable expectation of success, in that a POSA would have understood that increasing emulsifier levels means increasing surface area by reducing the size of individual oil globules. 136:10-137:11 (Rabinow). Reducing oil globule size means reducing PFAT5, referring to the percentage of fat globules greater than 5 microns. 213:20-214:4 (Rabinow). Thus, a POSA would have recognized that increasing emulsifier levels simultaneously helps keep an emulsion in place (avoiding crystals) and helps decrease PFAT5, justifying confidence in expecting to meet USP 1 and USP 729. 238:3-239:5 (Rabinow).

When answering questions about the reasonable expectation of success, Dr. Little consistently testified only that the claimed emulsifier levels and stability test results had not

already been reported in the prior art. 1321:21-1322:6, 1325:4-1326:1 (Little). But Dr. Little did not contest a POSA's reasonable expectation of success to go above CN845's 10% lecithin level. Both experts agreed that there will be an emulsifier level that would be "too high," although no level had been shown to be detrimental for any aprepitant formulation in the prior art. 167:16-168:5, 216:7-18 (Rabinow); 1286:14-1288:13 (Little). The prior art disclosed no upper boundary beyond which emulsifiers would not help aprepitant emulsions; in other words, there was no predetermined red line. 1426:14-1427:2 (Little). CN845 used 10% egg yolk lecithin, without any warning against higher levels. 242:22-243:5 (Rabinow.) CN845 also disclosed Examples using ratios of emulsifier-to-drug of up to 49:1. 245:18-21, 302:13-19 (Rabinow).

The CN845 autoclaving stability information, the Zhou K_e and other stability testing, and the POSA's knowledge about emulsifiers all support a reasonable expectation of success to make a physically stable aprepitant emulsion formulation.

F. Differences Between Prior Art and Claims at Issue

For purposes of trial, Heron asserted five claims, three from the '229 patent and two from the '794 patent. For the '229 patent, all asserted claims depend from unasserted claim 8, which recite the following aprepitant formulation components: 0.7 wt/wt% aprepitant, 14 wt/wt% egg yolk lecithin, 9-10 wt/wt% soybean oil, and sodium oleate (in any amount). JTX1.18. Claim 8 also requires a pH from 7.5 to 9.0. JTX1.18. Asserted claim 9 adds to claim 8 the requirement of 5 wt/wt% sucrose. Asserted claim 10 adds to claim 8 the requirement of 2-6 wt/wt% ethanol. Asserted claim 21 (which depends directly or indirectly on claims 8 and 17), refers to a method of treating nausea and vomiting with an intravenous formulation. JTX1.18.

Claims 9 and 10 of the '794 patent are the same as claims 9 and 10 of the '229 patent, except claims 9 and 10 add the "physically stable" requirement. The Court construed the "physically stable" term to require three stability tests at two temperature conditions, which align

with USP 1 and USP 729. *Compare* D.I. 176, Ex. 1 at ¶ 22, *with* JTX107.8; JTX120.3. A POSA would have been motivated, and had a reasonable expectation of success, to make a physically stable formulation as required by these claims, particularly in view of CN845 and Zhou.

CN845 disclosed ranges that included all of the claimed formulation components in the claimed amounts, with one exception: for lecithin, CN845 disclosed up to 10 wt/wt%, whereas the claims use 14 wt/wt%. Dr. Rabinow, Dr. Little, and the USPTO all reached this same conclusion. During trial, Dr. Little attempted to narrow the disclosures of CN845's Examples 7 and 8, testifying about wt/wt percentages he calculated based on a dilution step used to make an infusion. 1222:25-1223:19. But on cross examination, it became clear that CN845 disclosed both an "injection" (without dilution) and an "infusion" (with dilution). 1354:23-1359:2 (Little). That approach mirrored Dr. Little's own testimony about what later became Heron's commercial Cinvanti product, which uses both an "injection" (without dilution) and an "infusion" (with dilution). 1336:16-25, 1337:25-1338:13 (Little). Indeed, CN845's Examples 7 and 8 expressly listed the formulation amounts, which Dr. Little confirmed with a calculator added up to 100, so that the weight of each component also reflected the wt/wt% within the formulation. 1368:18-1369:21 (Little). The injection formulation in Examples 7 and 8 of CN845, it turns out, bracketed all of the claim limitations—again with the exception of 14% lecithin. 1362:7-1368:8 (Little).

A POSA applying routine optimization, based on CN845, Zhou, along with Washington and/or Liu, would have known to start with CN845 and use lecithin in amounts higher than CN845 did when optimizing the formulation specifically for USP physical stability. 218:13-25, 225:8-24 (Rabinow). The law is clear that routine optimization applies to this scenario, where the prior art disclosed operative ranges, disclosed that the lecithin level was a result-effective variable, and contained no objection for testing more than the 10% already used in CN845. *In re Peterson*, 315

F.3d 1325, 1329-30 (Fed. Cir. 2003). Importantly, the trial evidence showed no proof of criticality that the claimed 14% was special. To the contrary, Dr. Little admitted that Example 3 in the Patents-in-Suit used the lower 11.7% lecithin and still satisfied the Court's claim construction for a "physically stable" formulation. 1411:3-24 (Little).

All of the Asserted Claims would have been obvious to a POSA. The evidence showed that the claimed invention is obvious as a whole; CN845 provided all of the pieces in one formulation and the only modification to CN845 would have been to the emulsifier level. For convenience of analysis and comparing against the prior art as *Graham* requires, the claim limitations are addressed separately in this section.

1. CN845 disclosed aprepitant in a range that included the claimed 0.7% wt/wt% aprepitant (all Asserted Claims)

CN845 disclosed aprepitant emulsions, which included the range of "0.05-2% of aprepitant" in "percentage[] by mass." JTX71.13, ¶ 0008. Thus, CN845 disclosed the 0.7 wt/wt% aprepitant required in the Asserted Claims. *See* 227:18-228:14, 229:9-230:18 (Rabinow). In response to Fresenius Kabi's evidence, Heron did not respond with evidence of any criticality for the claimed aprepitant concentration. 1406:3-17 (Little). To the contrary, Dr. Little admitted that Example 4 from the Asserted Patents' specification reflected how a POSA would have applied CN845, (1401:21-1402:1 (Little)), and Example 4 used 0.672% aprepitant, which rounds to the claimed 0.7%, (JTX1.15); *see* D.I. 176, Ex. 1 at ¶23 (permitting rounding).

2. CN845 disclosed soybean in a range that included the claimed amount (all Asserted Claims).

The first inactive ingredient that CN845 discussed is the oil for the emulsion, and "preferably soybean oil." JTX71.13, ¶ 0010. A POSA would have understood that soybean oil was the preferred oil in pharmaceutical emulsions, as it was the "most used oil already commercially available in emulsions" giving it a "huge track record." 145:9-21 (Rabinow). In

addition, five of the eight Examples in CN845 used soybean oil. JTX71.14-17 (Examples 1, 4-7). The Zhou article also disclosed the use of soybean oil in its tested emulsions. JTX115.7, at 2.3.1. Moreover, the named inventors of the Patents-in-Suit both admitted that soybean oil "was a well-known component of oil-in-water emulsion" and that it "had been previously used…in parenterally administered emulsions." 473:4-6, 484:14-23 (Han); 550:18-551:3 (Ottoboni) ("Soybean oil was – has been used in emulsion formulations, yeah.").

CN845 also described the use of 5-30 w/w% soybean oil, which encompasses the claimed 9-10 w/w% soybean oil, and includes examples with 9-10% soybean oil. JTX71.17 (Example 7); 245:2-10 (Rabinow). From these disclosures, a POSA would have been motivated to use soybean oil and would have arrived at the claimed range of 9-10% using routine optimization within the range disclosed in CN845. In response, Heron did not assert any criticality for using soybean oil or using soybean oil in the amount claimed. 1407:14-24 (Little).

3. CN845 disclosed egg yolk phospholipid as the preferred emulsifier, and a POSA would have arrived at the claimed amount based on routine optimization, in view of Washington, Liu, and/or a POSA's knowledge (all Asserted Claims).

CN845 next disclosed the use of emulsifiers, and "preferably egg yolk phospholipid" for the aprepitant emulsion. JTX71.13, ¶ 0010; 146:6-13 (Rabinow). A POSA would have known that egg yolk phospholipid as an emulsifier was "in a class by itself," was commercially available, and was not associated with toxicity problems. 147:1-12 (Rabinow). Further, a POSA would have known that commercially marketed emulsions, such as Intralipid, used combinations of egg yolk phospholipid and soybean oil in oil-in-water intravenous emulsions. JTX84; 146:14-25 (Rabinow). This information would have further motivated a POSA to use a combination of soybean oil and egg yolk phospholipid as the oil/emulsifier combination in an emulsion and would have provided a reasonable expectation for successfully making an aprepitant emulsion using those

two core excipients. The named inventors of the Patents-in-Suit also admitted that egg yolk phospholipid was a known emulsifier when they started their work and that it "had a history of use in a number of pharmaceutical emulsions." 472:13-16, 483:20-484:2 (Han); 550:5-10 (Ottoboni).

As discussed above, the prior art teachings would have motivated a POSA to use additional egg yolk phospholipid, and, by engaging in routine optimization, a POSA would have arrived at the claimed amount of the emulsifier. From CN845, a POSA would have understood to use more emulsifier in an aprepitant emulsion because the preferred range of emulsifier in CN845 is approximately "eight times what the conventional levels of emulsifier are in commercially available emulsions." 155:20-156:15 (Rabinow). As Dr. Rabinow put it, this was the "novelty…with CN845": because aprepitant was not soluble in oil or water, CN845 taught creating a complex with the emulsifier and loading the complex at the interface between the oil and the water—"the only real estate available to accommodate the drug." 155:20-157:14 (Rabinow). A POSA would have also been aware of Khan and Washington, which would have motivated a POSA to use more emulsifier for an aprepitant composition. Khan taught "that the emulsion is the most important variable that drives stability of an emulsion." JTX91.5; *see also* 169:1-13 (Rabinow). Washington taught that in order to stabilize emulsions of Class III drugs like aprepitant, "you need a lot more emulsifier to generate the increased surface area so that you can situate your drug at that interface." 176:15-177:2 (Rabinow); *see also* 228:21-229:8 (Rabinow); JTX113.9.

With respect to the amount of egg yolk phospholipid, CN845 taught a preferred range of 8-10% (JTX71.13, ¶ 9); a POSA would have understood that adding emulsifier was a key to an aprepitant emulsion, and thus would have "focus[ed] in on the emulsifier level as a way to optimize his formulation work," (225:8-24 (Rabinow)). Zhou said the phospholipid both made an emulsion and "play the role of solubilization" in aprepitant emulsions. JTX115.11; *see also* 158:11-18,

217:9-218:12 (Rabinow). Khan showed that a POSA would determine "what is too low and what is too high" an amount of emulsifier. 167:20-168:5 (Rabinow); *see also* JTX91.5. Liu told a POSA "that he could go up as high as 30 percent in terms of phospholipid level," which was the "safest class of surfactants that [Liu] identified." 223:1-11 (Rabinow); *see also* JTX93.11; 228:15-20 (Rabinow) (discussing operative ranges). Through routine optimization, a POSA would have arrived at the claimed 14%: "[A] POSA would know that he would have to optimize and eventually wind up in a region containing 14 weight percent egg yolk lecithin because he would be sure to go up to something as high as 30 percent and he would look to see what is the point at which adding more lecithin no longer results in a benefit. So he would stop at that point." 229:9-230:18 (Rabinow). In addition, CN845 already disclosed high ratios of emulsifier to aprepitant, including working Examples that used up to 49:1 ratios. 245:18-246:5 (Rabinow). That range included the 20:1 ratio implied by the Asserted Claims. 1308:13-19 (Little). Thus, a POSA would have arrived at the claimed 14% emulsion by optimizing CN845 for USP in view of the teachings of Khan, Washington, and Liu. Once again, Heron did not assert any criticality for using egg yolk lecithin or using egg yolk lecithin in the claimed amount. 1408:21-1409:7 (Little). To the contrary, Example 3 from the Patents-in-Suit used 11.7% lecithin and still resulted in a physically stable emulsion for two months at room temperature and ten months when refrigerated. 1411:3-22 (Little); JTX7.15 (Example 3), .16 (Table 7).

4. CN845 and Zhou, in view of a POSA's knowledge, render the use of sodium oleate, a well-known pH adjuster and stabilizer, obvious (all Asserted Claims).

CN845 taught adjusting the pH of formulations; although CN845 did not list specific pH adjusters, a POSA would have understood that sodium oleate was an obvious and suitable choice for several reasons. First, a POSA understood that oleic acid was already a constituent part of egg yolk phospholipid, and that sodium oleate is the sodium salt of oleic acid. 201:12-202:5, 159:12-

160:5 (Rabinow); 1416:9-12 (Little); JTX84.1. Because the POSA was directed to basic formulations in both CN845 and Zhou, a POSA would have been motivated to select sodium oleate. 164:1-165:7 (Rabinow). Second, even if a POSA did not separately add sodium oleate, a formulation containing any sodium-based pH adjuster would create naturally-occurring sodium oleate contained therein, because as discussed above oleic acid is already a constituent part of egg yolk lecithin. 201:12-202:10, 377:24-378:4 (Rabinow). Thus, even using what Dr. Little testified was the most common basic pH adjuster, sodium hydroxide, a POSA would have understood that sodium oleate would still be part of the formulation. 159:12-160:5 (Rabinow); 1416:13-17 (Little). Third, the Zhou article disclosed adding oleic acid and touted additional benefits for using oleic acid. JTX115.7, .9, .11; 198:21-200:4 (Rabinow). Rather than adding oleic acid and then adding sodium hydroxide to get a basic pH, a POSA would have known to use sodium oleate instead, thereby both raising the pH and adding oleic acid at the same time. 424:18-425:8 (Rabinow).

Sodium oleate was such a common choice in emulsion work that prior art review articles called it out as commonly used with emulsions. For example, the Fell article, although dated just after the priority date, reflected the state of the art as of the priority date and reported that "[i]n addition to the phospholipid emulsifier, sodium oleate is added as a stabilizing agent." JTX76; *see also* 206:4-208:1, 425:3-8 (Rabinow). Wan, a patent application disclosing rolapitant emulsions, similarly declared that "[a]dditional stabilizers can be added including, for example, oleic acid or sodium oleate." JTX112.36, ¶ 0338; *see also* 427:25-428:22 (Rabinow). Jumaa further confirmed that sodium oleate had been commonly used in commercial parenteral formulations. JTX88.2; *see also* 437:22-439:10 (Rabinow). Jumaa also clarified that any hemolysis associated with sodium oleate was not an issue in the emulsion setting, particularly with egg yolk lecithin; this was "because the sodium oleate preferentially goes to the emulsion where it can enter the emulsion

membrane, and it's sequestered from interfering with the red [blood] cell." 383:10-385:2 (Rabinow); *see also* 429:15-430:16 (Rabinow). Especially given the fact that the Asserted Claims require no particular amount of sodium oleate, a POSA would have considered it an obvious choice to use in an emulsion formulation. Even if added for purposes of stabilizing an emulsion, a POSA would have understood sodium oleate would inherently adjust pH as well because "pH modification is an inherent characteristic of oleate." 231:13-24 (Rabinow).

While Dr. Little speculated that using sodium hydroxide instead of sodium oleate might cause reason for concern, he apparently had not reviewed Heron's own work that showed sodium hydroxide "instead of sodium oleate" worked just as well to create stable formulations. 1416:24-1419:11 (Little); DTX191_168. This outcome further demonstrates that there is no criticality for using sodium oleate, as opposed to any other pH adjuster. And as to the safety of choosing sodium oleate, Dr. Little did not even mention or rebut Dr. Rabinow's testimony on Fell or Jumaa.

Even during prosecution, Heron recognized that sodium oleate was just another excipient, and not a novel aspect of the claims in view of the prior art. When the Patent Examiner reported that CN845 disclosed pH adjustment, and that "any suitable compounds may be used," Heron did not respond saying that sodium oleate was new or unique. JTX2.88; 532:17-533:17 (Ottoboni). To the contrary, named inventor Dr. Ottoboni admitted that sodium oleate was known in the prior art and "was present in one other pharmaceutical formulation." 551:4-8 (Ottoboni).

5. CN845 disclosed a pH range, which overlapped with the claimed pH range (All Asserted Claims).

CN845 disclosed aprepitant emulsions with the pH range of 6.0 to 8.0. JTX071.13, ¶ 0011; *see also* 228:7-9 (Rabinow). Each of the Asserted Claims requires a pH range of 7.5 to 9. JTX1.18; JTX7.18; *see also* 228:7-9, 306:17-20 (Rabinow). A POSA would have understood that formulations containing aprepitant had been prepared within the pH range of 6.0 to 8.0 expressly

disclosed in CN845, and particularly in the basic range at or above 7.0. 230:16-18 (Rabinow).

No evidence showed criticality for the claimed range. The overlapping pH range disclosed in the prior art and the Asserted Claims renders obvious the pH limitation of the claims. *UCB, Inc. v. Actavis Laby's UT, Inc.*, 65 F.4th 679, 689-90 (Fed. Cir. 2023).

6. CN845 disclosed sucrose in a range that included the claimed amount (Claim 9 of '229 and Claim 9 of '794).

CN845 taught components that were "standard" for emulsions, including a "protective agent" to "ensure the correct tonicity with the blood." 134:6-18 (Rabinow); JTX71.8. Of the protective agents disclosed in CN845, sucrose would have been on the short list as an obvious choice. *See* JTX71.13; 148:14-19, 149:16-21, 149:22-151:5 (Rabinow). Sucrose was commonly used, and would not discolor the formulation at the appropriate pH range as disclosed by CN845. 148:20-149:15 (Rabinow). A POSA would have understood that CN845's protective agents were "osmotic agents," (139:6-9 (Rabinow)), that helped maintain tonicity for injectable formulations, (139:6-21, 140:3-141:6 (Rabinow)).

The amount of sucrose would have been obvious to the POSA as a matter of routine experimentation and optimization, and was within CN845's express disclosure. CN845 disclosed the range of 5-20% for the protective agent. JTX71.13. That range encompasses the 5% sucrose recited in claim 9 of the '229 patent and claim 9 of the '794 patent. 232:10-20 (Rabinow). All of the elements of claim 9 (of both Patents-in-Suit), taken together, would have been obvious because the prior art showed the claimed substances within a previously disclosed range, or showed that "a person of ordinary still would optimize for that particular level." 233:11-22 (Rabinow).

Heron did not assert that using sucrose as opposed to any other protective agent disclosed in CN845 makes a difference; nor would a POSA have understood the use of sucrose to make a difference. 232:21-25 (Rabinow). Once again, Heron did not respond with any evidence of

criticality. 1408:6-12 (Little).

7. CN845 disclosed ethanol in a range that included the claimed amount (Claim 10 of '229 and Claim 10 of '794).

It would have been obvious for a POSA to use a co-solvent in an intravenous emulsion, with ethanol being the obvious choice. CN845 taught the use of a co-emulsifier in aprepitant injectable emulsions, and listed limited options—ethanol, glycerol, 1,2-propylene glycol, polyethylene glycol 400. JTX71.13 [0010]; *see* 138:16-139:5 (Rabinow). CN845 also expressly disclosed that the co-emulsifier was "preferably ethanol." JTX71.13 [0010]; *see also* 147:13-18 (Rabinow). In the context of CN845, ethanol was the most compatible co-solvent because it had a suitable melting point for the step of dissolving the aprepitant and emulsifier and evaporating to allow them to come into proximity and form a complex. 139:1-5, 147:19-148:13 (Rabinow).

The amount of ethanol would have been obvious to the POSA as a matter of routine optimization, and was within CN845's express disclosure of 1-10% for co-emulsifier. JTX71.13; *see also* 233:2-10 (Rabinow); 1375:10-15 (Little). That range includes the 2-6% ethanol recited in claim 10 of the '229 patent and claim 10 of the '794 patent. 233:2-10, 233:23-234:7 (Rabinow). Heron's named inventor Dr. Ottoboni and expert Dr. Little both agreed that CN845's disclosures encompassed the claimed range. 528:23-529:6 (Ottoboni); 1368:5-8 (Little).

Heron did not produce any evidence of criticality. Dr. Little conceded that he provided no evidence regarding the impact on stability by using any other amounts of ethanol. 1408:13-20 (Little). Amounts outside of the claimed range of 2-6 wt/wt% (JTX1.18) exhibited stability, such as Example 1 of the Asserted Patents, which used 7.78 wt/wt% (JTX1.14) and was stable for two months at 25℃ and greater than 10 months at 5℃ (JTX1.16). Named inventor Dr. Ottoboni similarly admitted that formulations containing various amounts of ethanol that were tested during development were all physically stable for more than 20 days. 551:13-21 (Ottoboni).

8. CN845 disclosed intravenous treatment of nausea and vomiting (Claim 21 of '229).

Claim 21 of the '229 patent refers to the formulation variables of claim 8, and is directed to the method of use for treating nausea and vomiting. JTX1.18. Heron did not dispute the prior art showed an infusion with beyond a reasonable expectation of clinical efficacy. Zhou's title was "Preparation of Aprepitant Emulsion for Intravenous Injection." JTX115.1. CN845 specifically disclosed formulations "suitable for intravenous administration clinically." JTX71.14 [0015]. CN845 also expressly reported "aprepitant had better efficacy in preventing acute and delayed CINV." JTX71.11 [0003]; *see also* 141:23-143:4 (Rabinow). A POSA would have expected the efficacy of an intravenous aprepitant formulation in view of the already-established oral aprepitant product and because there is no metabolism of the drug with IV administration. 590:8-591:14 (Markman). Dr. Roeland similarly agreed that "when you give an IV, we know that patients are going to get the drug." 1016:17-1018:7 (Roeland). As Dr. Little conceded, there is no dispute as to this claim apart from the formulation limitations: "from my understanding, aprepitant, if it was put into a stable formulation for intravenous use, could be used to treat nausea and vomiting." 1434:15-1435:5 (Little). Claim 21 added nothing new or unexpected to the prior art.

9. With routine optimization, a POSA would have reasonably expected a "physically stable" formulation as required by the asserted claims of the '794 patent (Claims 9 and 10 of '794).

Asserted Claims 9 and 10 of the '794 patent recite the same formulation limitations as claims 9 and 10 of the '229 patent, and require an additional "physical stability" limitation. This additional limitation also does not change the obviousness of claims 9 and 10 of the '794 patent. Importantly, the duration for a "physically stable" formulation as claimed in the '794 patent is for only "at least one week"; therefore, the only threshold is that a product must be expected to meet the claimed stability criteria for one week, or seven days. D.I. 176, Ex. 1 at ¶ 22; *see also* 293:3-

16 (Rabinow); 1403:1-10 (Little).

As discussed above, CN845 disclosed excipients to formulate aprepitant emulsions, including a pH adjuster. The POSA would have been motivated to test emulsifier ranges up to 30% as part of routine optimization for achieving USP standards. USP 1 and USP 729, in particular, relate to injectable formulations, including emulsions. JTX107; JTX120. USP 1 includes visible crystal standards, and USP 729 includes PFAT5 and particle size standards. Those USP standards align with the Court's claim construction for a "physically stable" product. *Compare* D.I. 176, Ex. 1 at ¶ 22, *with* JTX107.8; JTX120.3; *see also* 211:9-16, 212:8-20, 213:20-214:4 (Rabinow). A POSA would have known they needed to meet these requirements in order to achieve a stable formulation eligible for FDA approval and commercialization of an intravenous aprepitant formulation. It was undisputed that a POSA's knowledge included USP stability standards, that meeting those standards was required for commercialization, and that stability testing was considered routine. 208:8-22 (Rabinow); 1267:1-1268:7, 1393:7-14 (Little); 521:16-522:6 (Ottoboni); 468:10-21, 508:17-509:11 (Han).

A POSA would have had a reasonable expectation that an aprepitant emulsion formulation would result in a "physically stable" product. Specifically, consistent with the Court's construction of that term, a POSA would have had a reasonable expectation that an aprepitant formulation would be stable with respect to: (a) particle size, (b) PFAT5, and (c) no visible crystals. For instance, CN845 reported emulsions were made, even after applying a "stress," and showed that they survived autoclaving. 246:9-18 (Rabinow); JTX71.16-.17. Zhou optimized a proposed aprepitant formulation based on the K_e variable, but then also reported a battery of stability tests for the proposed formulation. JTX115.10 (Table 4); *see also* 202:16-204:13 (Rabinow). Even Dr. Little testified that Zhou used K_e, which "gives you some stability criterion," which he understood to be

different from USP. 1268:16-1269:3 (Little). CN845 and Zhou demonstrated to a POSA that aprepitant emulsions were physically stable, and gave confidence to a POSA that they could meet the USP standards for physical stability. 194:6-22 (Rabinow).

Indeed, the prior art expressly met the USP 729 requirement for particle size less than 500 nm. JTX120.4; 212:8-20 (Rabinow). CN845 described particle sizes in the range "50 nm – 150 nm." JTX71.13 at [0012]; *see also* 238:3-239:5 (Rabinow). Zhou reported a "220.3 nm" particle size. JTX115.10 Table 4; *see also* 202:24-203:9 (Rabinow). Zhou showed that the particle size did not change for 3 months, either stored at room temperature or refrigerated temperature. *Id*. Dr. Little agreed that Zhou showed aprepitant emulsion formulations that met the particle size requirement for USP 729 and the "physically stable" claim limitation. 1395:6-12 (Little).

The prior art gave confidence that the PFAT5 requirement would be met. The PFAT5 requirement refers to the percentage of fat globules that are above 5 microns, which must be less than .05%, reflecting a USP 729 standard. JTX120.6; 213:20-214:4 (Rabinow). Because Zhou optimized for K_e, a POSA would have understood Zhou had not yet optimized for USP 729; as such, Zhou did not report a PFAT5 result. 213:20-214:17 (Rabinow). But based on the small particle size results from CN845 and Zhou, "there would be a very high degree of expectation of meeting PFAT5 as well, although, that would, of course, have to be separately demonstrated." 238:3-239:5, 136:10-137:11, 356:15-357:14 (Rabinow). A POSA would have further understood that increasing the amount of emulsifier for the purpose of increasing surface area, as discussed above, would at the same time decrease oil globule size; further supporting the POSA's reasonable expectation of successfully meeting the PFAT5 requirement. 135:19-136:5 (Rabinow). Dr. Rabinow explained a POSA, based on CN845, would have understood that increasing emulsifier will reduce particle size. 163:7-19 (Rabinow). Dr. Little also admitted that increasing emulsifier

"will allow you to make a globule size potentially that is smaller than before." 1426:1-13 (Little). Dr. Little noted that Zhou did not report a PFAT5 result (1266:24-25 (Little); however, he did not rebut Dr. Rabinow's testimony about the POSA's reasonable expectation for meeting PFAT5.

Finally, as to visible crystals, CN845 and Zhou again provided a POSA with a reasonable expectation of success to achieve a "physically stable" formulation. For this requirement, the Court's construction referred to visible crystals "when viewed at magnification of 4x to 10x." D.I. 176, Ex. 1 at ¶ 22. Applying the Court's construction properly, a POSA would have understood that 4x to 10x is a "trivial" requirement given the low magnification level. 239:6-13 (Rabinow). Dr. Little similarly explained that aprepitant crystals are not visible under 4x to 10x magnification, and confirmed that he had "never seen one test that shows a crystal at an actual magnification of 4x to 10x." 60:17-22, 72:23-73:20 (Little). Dr. Little failed to rebut the reasonable expectation of success; rather, he only noted that the prior art did not report whether aprepitant crystals were observed, although he conceded that Zhou's K_e was a "measure of stability" and "has to do with things like flocculation, coalescence, and things," (1396:21-1397:4).

Dr. Little offered his view that the Court's construction referred only to an "objective lens" within that range, which coupled with an eyepiece lens would mean a higher actual magnification. 69:13-23 (Little). Dr. Little asserted that the "standard eyepiece is 10x," and then alleged that the actual "total magnification requirement is 100x." *Id*. Even using that interpretation, which is not consistent with the Court's construction, Dr. Rabinow explained that a POSA would have had a reasonable expectation of success based on the Zhou data. 241:15-25 (Rabinow). Zhou emphasized the importance of assessing crystal formation, and reported that "the presence or absence of crystals can be used to determine whether de-emulsification takes place." JTX115.12; *see also* 238:3-239:5 (Rabinow). The Zhou article also expressly reported that "no stratification

or de-emulsification was detected." JTX115.10. The reference did not expressly state that no crystals were formed; however, a POSA would have understood in the context of the reported data that if crystals had been seen, then they would have been reported. 238:3-239:5 (Rabinow).

10. Alternatively, the "physically stable" limitation is inherent to the claimed formulation (Claim 9 and 10 of '794).

In addition, and as an independent basis for meeting the "physically stable" claim limitation of the two asserted '794 patent claims, a POSA would have understood "physically stable" is an inherent property of the formulation. A reasonable expectation of success is not separately required for an inherent property. *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1331-32 (Fed. Cir. 2020). Dr. Little agreed that stability is a property of a formulation, (64:8-14 (Little)); in fact, he acknowledged that he used Heron's Cinvanti product testing to show Fresenius Kabi allegedly infringed "because the formulations were the same," (56:11-19 (Little)). If the Court adopts Plaintiff's position on infringement relevant to the "physically stable" limitation, that position supports this limitation is inherent for obviousness purposes. As discussed above, a POSA would have been motivated to routinely optimize the CN845 formulation, by increasing emulsifier levels to increase physical stability (to meet USP requirements), and with the knowledge that levels of up to 30% lecithin could be used as part of routine optimization. In so doing, the POSA would have reached 14% lecithin as a matter of routine optimization to meet USP stability. The POSA would also have necessarily achieved the "physically stable" formulation, since stability is a property of the formulation itself. 237:21-238:2, 248:25-249:14 (Rabinow).

V. Secondary Considerations Did Not, and Cannot, Overcome the Strong Showing of Obviousness

While secondary considerations must be considered as part of an obviousness analysis, "they do not necessarily control the obviousness determination." *Bristol-Myers Squibb v. Teva Pharms. USA*, 752 F.3d 967, 977 (Fed. Cir. 2014). Fresenius Kabi provided a strong showing of

obviousness, particularly in view of CN845 and Zhou, which favorably disclosed aprepitant emulsions that required only routine optimization. The evidence on secondary considerations that Heron presented does nothing to change that fact. Indeed, Heron failed to show a nexus to any novel features of the Asserted Claims, and instead relied upon features "known in the prior art" including CN845 and Zhou. *Merck & Cie v. Gnosis S.p.A*, 808 F.3d 829, 838 (Fed. Cir. 2015). In a case like this one, "weak secondary considerations generally do not overcome a strong prima facie case of obviousness." *W. Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1373 (Fed. Cir. 2010) (citations omitted); *see also Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1371 (Fed. Cir. 2011) ("A strong case of prima facie obviousness . . . cannot be overcome by a far weaker showing of objective indicia of nonobviousness."); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007) (finding that even "substantial evidence of commercial success, praise, and long felt need" was "inadequate" to overcome a strong prima facie showing of obviousness). Taking into account all of the secondary considerations, the Asserted Claims would have been obvious to a POSA.

A. The Asserted Claims Reflect No Unexpected Results

First, to show any result is "unexpected," Heron had the burden to first provide "evidence of what the skilled artisan would have expected," and then show that the claimed formulations went against that expectation. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). Heron failed to do so. Dr. Little provided no evidence of what a POSA would have expected based on the prior art, and on cross examination conceded that there was no basis to form any expectation because "[b]efore you do the test, if you look at CN845, there's no information on stability." 1433:21-1434:14 (Little). Because Heron did not allege what would have been ***expected*** based on the prior art, Heron cannot meet the threshold requirement to allege any ***unexpected*** result.

Moreover, the only alleged unexpected result was based on comparisons between internal

tests that Heron did on its own, not on what a POSA would conclude from public prior art. Dr. Little asserted that prior art formulations were "found to be nonstable" because Heron allegedly made reproductions of the prior art and, when tested, found crystal formation at four days; whereas "the formulations in the patents-in-suit, those were stable" for at least seven days. 1344:25-1345:11 (Little). Heron included those test results as Examples 4 and 5 of the Patents-in-Suit, which Dr. Little admitted were not prior art. 1400:25-1401:20 (Little). It is legally improper to rely on "what the inventor knew at the time of the invention" to show any supposedly unexpected result. *Bristol-Myers*, 752 F.3d at 978.

Next, there was nothing "unexpected" about increasing emulsifier level to increase stability, which is all that Heron appears to allege. 1344:20-1345:7 (Little). Dr. Rabinow explained at length the many reasons that a POSA would have reasonably ***expected*** increased stability with increasing emulsifier level, including increased surface area, decreased globule size, and complex formation. 136:10-137:11, 151:10-152:16, 173:19-175:14, 176:15-178:3, 356:15-357:2 (Rabinow); *see also* JTX113.4. In response, Dr. Little did not agree that complex formation had been proven; however, he did agree that adding emulsifier increased surface area and decreased globule size, (1425:14-1426:13 (Little)). Dr. Little also acknowledged that there is some undetermined inflection point beyond which adding emulsifier would not help (1286:14-1288:13 (Little)); relying on Khan, Dr. Rabinow explained a POSA would have understood that they could determine how much emulsifier to help improve stability through routine optimization, (167:16-168:5, 168:11-169:13, 216:7-18 (Rabinow); *see also* JTX91.5). Dr. Little did not rebut Dr. Rabinow's opinion that increasing emulsifier levels would be ***expected*** to increase stability at least up until some point; as such, Dr. Little's unexpected results opinion is unsupported. *Bristol-Myers*, 752 F.3d at 978 (affirming obviousness because evidence showed "one of skill in the art would

have expected" the asserted unexpected results); *see also Adapt Pharma Ops. Ltd. v. Teva Pharm. USA*, 25 F.4th 1354, 1373-74 (Fed. Cir. 2022) (affirming obviousness where POSA would expect that "using a permeation enhancer such as BZK would result in increased bioavailability").

In addition, Heron's unexpected results comparisons—using Example 4 of the specification of the Patents-in-Suit to represent CN845 and Example 5 to represent Zhou—failed to compare the Asserted Claims to the closest prior art, another requirement for showing unexpected results. *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 97 F.4th 915, 933 (Fed. Cir. 2024) (citing *Bristol-Myers*, 752 F.3d at 978). The main problem with the comparisons is that they failed to control for pH. CN845 reported the suitable pH range of 6.0-8.0, but Example 4 only used the pH of 7.0. Meanwhile, the claimed pH range is 7.5 to 9.0, so by only testing CN845's pH of 7.0, Heron could not have distinguished the prior art from the claimed formulations; rather, it would have needed to test both at the same pH range(s). 286:6-17 (Rabinow). Heron also did not use any of the actual Examples from CN845. 490:17-20 (Han); 290:12-18 (Rabinow). But even for the experiments Heron did undertake, failing to use the same pH precludes any apples-to-apples comparison. 292:23-293:2 (Rabinow). Similarly Zhou expressly reported a pH of 7.31, but Heron did not report any pH in Example 5. JTX115.10; JTX1.15-.16 (Example 5); *see also* 290:24-291:2, 292:15-22 (Rabinow). The underlying lab notebook associated with the Zhou article "duplicat[ion]" showed that a pH of 6.5 had been used, which once again could not have provided a fair comparison between the prior art and the Asserted Claims. DTX190_3; 501:1-10, 503:1-13 (Han); 1419:12-1421:1 (Little). Heron's own patent specification showed that pH mattered, and the only working Examples of the Patents-in-Suit that disclosed physically stable formulations (Examples 1, 2, 3, and 6) "were all formulated at a pH of around 8.7 to 8.8, whereas the CN formulations were formulated around pH 7." 286:6-287:6 (Rabinow); *see also* JTX1.16-17 (Table

7); JTX71.14-.17 (Examples 1-8). For these reasons, the patent specification comparison "was not a controlled experiment to any extent." 289:20-25 (Rabinow).

Finally, Heron's unexpected results argument relates to a difference in degree and not kind. "When assessing unexpected properties, therefore, [courts] must evaluate the significance and 'kind' of expected results along with the unexpected results." *Bristol-Myers*, 752 F.3d at 977 (comparing example of difference in degree of "more potent" drug with example of difference in kind of novel "antiviral activity"); *Adapt*, 25 F.4th at 1374. Even if Examples 4 and 5 had provided appropriate comparisons, they still show that the CN845 and Zhou formulations were stable for four days. That compares to the Asserted Claims, which require physical stability for "at least a week," resulting in a difference of just three days – "a question of degree rather than kind." 293:3-22 (Rabinow). Even assuming comparisons to longer periods of time, the only comparisons Heron offered reflect a "matter of degree." 293:23-294:6 (Rabinow).

B. The Asserted Claims Do Not Satisfy Any Long-Felt Unmet Need

Heron never met the legal or factual requirements for showing any long-felt but unmet need. Heron's alleged long-felt need is for an NK-1 receptor antagonist that, compared to Emend IV, was "equally as efficacious with fewer related side effects." 1058:17-1059:2 (Roeland). But Heron failed to show that this was a demonstrated need, that medical practice failed to manage side effects, or why CN845 and Zhou did not already meet any supposed need.

1. Heron never established an articulated need, much less one that was long-felt.

The law "requires that [patentee] submit actual evidence of a long-felt need, as opposed to argument." *In re Kahn*, 441 F.3d 977, 990-91 (Fed. Cir. 2006). To show long-felt need, Heron relied on assertions without "evidence to explain how long this need was felt, or when the problem first arose." *Perfect Web Techs. Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1332-33 (Fed. Cir. 2009).

Here, as in *Perfect Web*, Heron assembled various after-the-fact differences between the prior art and Cinvanti, which at most showed "drawbacks" of the prior art, but not any "long-felt, unmet need alleviated by the patent." *Id*.

Heron did not identify any particular problem or efforts to solve any problems with Emend IV between that drug's approval in 2008 and the 2014 priority date for the Patents-in-Suit. In fact,

[redacted]

[redacted] Moreover, large-scale prospective studies showed Emend IV only caused about 2-3% infusion site issues, and any hypersensitivity reactions were "isolated." JTX73.5, .8; 604:11-605:20, 666:17-668:1 (Markman). Without evidence of any recognized issue, "it goes without saying that there could not possibly be any evidence of either a long-felt need . . . or failure of others. . . ." *In re Gershon*, 372 F.2d 535, 539 (C.C.P.A. 1967).

2. Heron never established the cause for any potential side effect issue with Emend IV.

Heron's analysis is further flawed because its experts did not establish the cause for potential side effects experienced with a chemotherapy regimen that includes Emend IV; thus, Heron failed to show the claimed invention made any difference. As Dr. Markman testified, reported causes for side effects, including those about which Dr. Roeland testified, included (1)

the use of vesicant chemotherapy, which was known to cause local toxicity, (609:17-612:16 (general); 620:18-621:4 (regarding JTX137.5); 627:11-628:8 (regarding JTX134.3); 634:9-635:12 (regarding JTX138.3); 647:1-21 (regarding JTX154.3)); (2) the use of a peripheral line in administering the drugs which can lead to reactions unrelated to Emend IV, (612:17-617:2 (general); 621:21-623:16 (regarding JTX137.5); 628:20-629:6, 630:4-12 (regarding JTX134.4); 635:16-636:5 (regarding JTX138.3)); and (3) the use of high drug concentration, (642:13-643:17 (regarding JTX146.7)). As Dr. Markman explained, the Leal reference expressly confirmed that side effects were attributable to patients "who receive AC chemotherapy via peripheral line as opposed to a central venous device, which is used by a majority of patients receiving AC chemotherapy in many practices." 621:21-622:10 (Markman); *see also* JTX137.5. Dr. Roeland similarly admitted that the Navari article correctly assessed that "it can be difficult to distinguish adverse events related to antiemetics *from those associated with chemotherapy*." JTX139.11 (emphasis added); 1087:10-25 (Roeland). Heron's experts never rebutted Dr. Markman's showing that "there is no way you can draw any conclusions related to fosaprepitant as a cause of [the] reactions," 625:12-18 (Markman); *see also* 617:3-9, 630:23-631:18, 636:18-637:3, 645:7-12, 647:1-11, 654:18-655:14 (Markman).

Dr. Markman also explained that every one of the articles Dr. Roeland cited involved retrospective analyses, on which a POSA would not have reasonably relied to make conclusions regarding the source of inconsistently reported issues like infusion site reactions. 607:21-609:16, 739:6-741:13 (Markman). Indeed, the Leal analysis expressly noted the "relatively standard limitations with respect to retrospective study designs," including "underreporting, overreporting, or simply inadequately documenting toxicity data." JTX137.5; 623:17-624:7 (Markman). The other retrospective analyses each contained similar disclaimers, discrediting the value of the

proposition that Dr. Roeland was trying to assert, i.e., that there was a long-felt need associated with Emend IV. *See* JTX134.5; 631:4-13 (Markman (noting "well known" limitations including "lack of prospective reporting")); JTX138.6; 640:4-21 (Markman (discussing "possibility of information bias" and "instances where there was missing information" or poor documentation); JTX146.8; 643:18-644:25 (Markman (testifying "[t]hey didn't even have information to be able to say when the reaction occurred relative to when the fosaprepitant versus when the chemotherapy was given")); JTX154.5; 648:9-649:5 (Markman (discussing "retrospective in nature with inherent challenges of interpreting medical records with regards to infusion site reactions")); JTX127.8; 656:18-658:23 (Markman (discussing retrospective that showed equivalence between Emend IV and Cinvanti)). Another problem with relying on the retrospective studies is small sample size; even Dr. Roeland admitted with respect to Hegerova that the sample size, 81 patient records, was "too small a sample size to determine if there's any actual effect." 1101:11-24 (Roeland).

Without a prospective study designed to see if there are any demonstrable differences between Emend IV and Cinvanti, no alleged difference can be medically justified. 601:14-603:20, 739:6-741:13 (Markman). The prospective study described in the Emend IV label reported only 2.2% and 3% infusions site adverse reactions with Emend IV. JTX73.8; JTX134.5; JTX138.2. Dr. Roeland did not dispute that data, and indeed admitted that Weinstein reported that "[n]one of [the] infusion-site reactions were considered by the investigator to be severe or related to [fosaprepitant products]." 1092:22-1094:17 (Roeland); DTX74_2.

3. Any alleged need was already addressed because physicians knew (and still know) how to administer Emend IV to reduce reaction risks.

Every article on which Dr. Roeland relied—and ones on which he did not rely—showed doctors had tools to manage the potential risk of reactions when administering any chemotherapy regiment, including with Emend IV. Evidence of long-felt need is not probative if "others had

previously solved the long-felt need," even if not in the same way as the claimed invention. *In re PepperBall Techs., Inc*., 469 F. App'x 878, 882 (Fed. Cir. 2012); *see also ABT Sys., LLC v. Emerson Elec. Co.*, 797 F.3d 1350, 1362 (Fed. Cir. 2015) (granting JMOL of obviousness where "disclosures of the prior art references...eliminate any serious contention that there was a long-felt need" for the claimed invention). In *ABT*, the Federal Circuit held that the prior art addressed the benefits allegedly provided by the claimed periodic fan operation function for HVAC systems, though the prior art achieved such operation in a different way than the claims. *ABT*, 797 F.3d at 1355, 1362. Similarly here, Dr. Markman showed that the articles Dr. Roeland cited already provided medical solutions to any perceived problems. For example, to reduce or eliminate the risk of reactions with Emend IV, physicians used non-vesicant chemotherapy (JTX134.1), administered medications through a central line (623:11-16, 630:13-22, 640:22-641:9, 648:9-16, 654:24-655:14 (Markman); JTX127.8, JTX154.5), used a lower concentration of fosaprepitant or diluted it more (642:22-643:17, 664:19-665:19 (Markman); DTX35_1), and administered fosaprepitant in the same bag as dexamethasone (665:20-666:13 (Markman); DTX35_3; 654:8-17 (Markman); JTX127.5). Heron never substantiated a "problem" with Emend IV, because physicians knew how to manage its administration. In fact, Dr. Roeland agreed Emend IV and generic fosaprepitant are "still used by doctors today" (1081:14-19 (Roeland)), confirming that there was no long-felt, unmet need.

Dr. Roeland only responded to one of the several medical approaches that Dr. Markman identified was already used to address potential injection site reactions or hypersensitivity issues. Dr. Roeland asserted that the central port approach might not be suitable for every patient. 1055:4-18 (Roeland). But he did not allege a need to help that narrow set of patients existed, much less why the claimed invention would avoid side effects when given peripherally. Further, Dr. Roeland's cited articles show that a vast majority of patients are administered regimens through a

central line. JTX127.8 (85% of patients in study used a central line); JTX137.5 (noting central line used for "majority of patients"); JTX150.3 (central line used with 86% of patients in study); 621:21-623:8, 654:24-655:14, 662:15-663:7 (Markman). And those patients receiving treatment through a central line did not experience reactions. *See, e.g.*, JTX134.4; 630:4-22 (Markman). Dr. Roeland's cited articles thus support Dr. Markman's testimony that a central port was known to be much safer and has been the standard of care for all treatment regimens for decades, especially those involving vesicant chemotherapy. 613:15-617:2, 621:21-623:8 (Markman). Even for any patients who for some reason cannot have a central port, and require peripheral vein administration, Dr. Roeland did not address why any of the alternative available solutions were inappropriate.

4. Heron never showed that Cinvanti solved any need.

Because Dr. Roeland never identified any need to begin with, he certainly failed to show how Heron's commercial product Cinvanti solved any alleged need. Instead, Dr. Roeland compared the Emend IV and Cinvanti labels, and pointed out that there was a difference in warnings: Emend IV warned about potential injection site reactions and Cinvanti did not. 1065:24-1066:12. But there was no evidence that "injection site reactions" were ever actually reduced with Cinvanti. To the contrary, the Dranitsaris article compared rates of adverse events associated with fosaprepitant formulations and Cinvanti. Dr. Markman testified (unrebutted) that the Dranitsaris article showed the safety and efficacy of the products were "the same." 653:9-654:23 (Markman); *see also* JTX127.5. So merely pointing to a difference in labels means nothing about whether there was any need to begin with, or how the alleged invention is connected with the change in labels.

Dr. Roeland tried to argue that Cinvanti met a long-felt need for reduced use of rescue medication, referring to the 2022 Dranitsaris article. 1062:3-9 (Roeland). Dr. Roeland never demonstrated an articulated need in the prior art, or why rescue medication related to the alleged invention. And ultimately Dr. Markman testified, without rebuttal, that Dranitsaris reported no

statistical difference in the use of rescue medications between Cinvanti and available generic fosaprepitant alternatives. 658:24-659:2 (Markman); JTX127.5.

Based on the time spent discussing polysorbate 80, Heron might try to contend that polysorbate 80 and "injection site reactions" are somehow related. But there was no evidence presented supporting a correlation between polysorbate 80 and injection site reactions. Dr. Markman testified that "there is no biological or clinical link between hypersensitivity reaction and infusion site reaction." 599:19-601:1, 648:2-8 (Markman). If polysorbate 80 was associated with anything, it was hypersensitivity reactions, which are systemic allergic reactions and not "injection site reactions." 669:20-674:8 (Markman); JTX126.1; JTX138.5; JTX148.7. Dr. Markman also showed that Dr. Roeland and the articles he referenced failed to show any hypersensitivity reactions caused by the polysorbate 80 in Emend IV. *Id*.; *see also* 648:2-8 (Markman). [redacted] Fatal to Heron's position is that both the Emend IV label and the Cinvanti label contain the same hypersensitivity warning. *See* 668:2-669:15 (Markman); JTX129.6; JTX51.5. Cinvanti changed nothing regarding the hypersensitivity reactions reportedly associated with polysorbate 80.

Ultimately, as Dr. Markman testified, even though polysorbate 80 did not present a "long felt, unmet need," still a doctor "is always looking for better drugs." 705:8-21 (Markman). In *Spectrum Pharms., Inc. v. Sandoz Inc*., 802 F.3d 1326 (Fed. Cir. 2015), the Federal Circuit affirmed the obviousness of claims to a purer drug product that helped reduce toxicity. The court

acknowledged the motivation to purify the prior art mixture and avoid the undesirable isomer, but found that there was no long-felt need since the claimed purified isomer compound was shown to be clinically interchangeable with the unpurified prior art product. *Id*. at 1336. The same is true here. While there may have been a motivation to avoid polysorbate 80, Cinvanti remains clinically interchangeable with Emend IV both in terms of safety and efficacy. JTX127.5; 653:9-654:23, 668:2-669:15 (Markman); JTX129.6; JTX51.5. Cinvanti's own FDA approval was based on bioequivalence to Emend IV, and not on any new clinical trials or studies demonstrating Cinvanti was somehow safer than Emend IV. 522:13-523:5 (Ottoboni); 1081:24-1082:15 (Roeland).

5. CN845 and Zhou already met any long-felt need.

Finally, if there was any long-felt need to reduce side effects with Emend IV, then that need was already addressed in 2012 by CN845 and Zhou. If the prior art already solved the alleged need, then Heron's assertions could not be "sufficiently connected with the novel elements of the asserted claims." *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 838 (Fed. Cir. 2015). Here, each of the Asserted Claims uses the "comprising" transition phrase and permits polysorbate 80, one more reason that Heron failed to show any nexus. *See* JTX1.18; JTX7.18. To the extent that Heron's underlying position is that polysorbate 80 is associated with problems, and that Cinvanti does not use polysorbate 80, then CN845 and Zhou already solved that alleged need. Dr. Markman and Dr. Rabinow showed that a POSA would have been motivated to avoid the use of polysorbate 80 in an aprepitant formulation (666:17-667:18, 705:8-21, 708:3-24 (Markman); 125:17-22, 147:1-12, 235:9-18, 252:23-253:3 (Rabinow)); CN845 provided polysorbate 80-free formulations for IV aprepitant emulsions (253:4-18, 255:3-8 (Rabinow); JTX71.14-17). The Zhou article did not use polysorbate 80 in its formulations. So these prior art aprepitant emulsions already met any alleged need for polysorbate-free formulations. Dr. Little knew about both CN845 and Zhou, but failed to address them in his analysis regarding any supposed long-felt need. 1436:6-10 (Little).

Where, as here, the differences between the prior art and the claimed invention are minimal, "it cannot be said that any long-felt need was unsolved." *Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304-05 (Fed. Cir. 2010).

C. The Asserted Claims Did Not Relate to Any Failure of Others

To show failure of others, Heron should have shown how those in the prior art tried but failed to develop the claimed invention. *See, e.g.*, *In re Couvaras*, 70 F.4th 1374, 1381 (Fed. Cir. 2023). Given the significance of CN845 and Zhou, Dr. Little asserted that he deemed these references to be failures simply because they were not shown to have been separately commercialized. 1435:13-21 (Little). Whether or not the formulations were commercialized is irrelevant. The state of the art included CN845 and Zhou, and they showed working and stable aprepitant emulsions. 246:9-18 (Rabinow), JTX71.14 at [0017]; 204:7-12 (Rabinow), JTX115.5, .10. Those references showed successes, not failures. Heron's expert Dr. Hale admitted that publications are not considered "failures simply because they did not proceed to clinical development." 986:21-987:4 (Hale). And Dr. Little admitted that "I don't think that there was data [in CN845 or Zhou] showing that there was a failure." 1402:12-20 (Little). Heron never showed any failure of others to develop an aprepitant emulsion, and certainly showed no failure after CN845 was published in 2012, showing once again that CN845 already succeeded. *See, e.g.*, *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966) ("At the latest, those differences were rendered apparent in 1953 by the appearance of the Livingstone patent, and unsuccessful attempts to reach a solution to the problems confronting Scoggin made before that time became wholly irrelevant.").

The only other testimony Heron presented is that Merck did not develop an aprepitant emulsion formulation, and made an oral aprepitant formulation and an injectable fosaprepitant formulation. 1347:7-1348:13 (Little); 913:4-9, 966:2-9, 971:22-25 (Hale). There was no evidence of any failure. Indeed, there was no evidence of any formulation efforts that Merck undertook,

much less any reported failure, to make an aprepitant emulsion in particular or any injectable aprepitant solution more generally. 990:16-991:14 (Hale); 255:24-256:2 (Rabinow). Dr. Hale admitted he was a medicinal chemist, and not a formulator, and did not work on formulations at Merck. 969:21-23, 972:4-8 (Hale). At trial, Dr. Hale cited to three references lauding Merck's medicinal chemistry efforts in NK-1 receptor antagonists: Hargreaves (JTX82), Hale (PTX3), and Meurer (PTX15), each of which noted Merck knew that aprepitant had low water solubility, not that Merck tried and failed to make any other injectable formulation. 971:22-25 (Hale). In fact, aprepitant's low water solubility is an inherent property of the molecule, and Heron did not solve that problem. Dr. Little admitted that he did not present any publications regarding any information in the prior art about Merck's formulation efforts. 1399:14-1400:4 (Little). All the evidence showed is that Merck knew that aprepitant was not water soluble, and that Merck designed a water-soluble prodrug called fosaprepitant. Merck synthesized both aprepitant and fosaprepitant in 1993. JTX82.7.

D. The Formulations of the Asserted Claims Were Not Met with Skepticism

It is unclear if Heron is alleging skepticism. Heron discusses skepticism in the Pretrial Order; however, at trial, its witnesses never uttered the word or presented any evidence to support this secondary consideration. For that reason alone, Heron failed to meet its burden of proof to support a skepticism allegation.

Moreover, to show skepticism, Heron had to have shown third-party experts in the field who had evaluated aprepitant solutions, and in particular the claimed aprepitant emulsions, and reported some actual doubt about their ability to work. *See, e.g.*, *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013). Skepticism that is not directed at the solution provided by the patented invention "is not the type of skepticism that amounts to evidence of nonobviousness." *In re Youngblood*, No. 98-1518, 1999 WL 504243, at *11 (Fed. Cir.

July 6, 1999). Heron did not offer any such evidence, and certainly did not offer any evidence calling into question aprepitant formulations after CN845 was published.

To the extent that Heron intends to rely on Dr. Hale's testimony, Dr. Hale is not equipped to offer any opinion about skepticism (or any substantive issues in this case). He is not a formulator. 972:4-8 (Hale). He is not a POSA. 967:21-969:23 (Hale). And the references he cited were medicinal chemistry publications, noting that aprepitant was not soluble in water. PTX3; PTX15. As Dr. Rabinow testified, a POSA would not have been skeptical about making a soluble and stable formulation of aprepitant by the 2014 priority date, since CN845 and Zhou already made them. 273:15-274:9 (Rabinow).

E. Alleged Copying Is Not Probative in a Hatch-Waxman Case

Evidence of copying is not probative of nonobviousness in the context of the Hatch-Waxman Act and the filing of an ANDA. *See Adapt*, 25 F.4th at 1374; *Bayer*, 713 F.3d at 1377; *Purdue Pharma Prods., L.P. v. Par Pharm., Inc.*, 377 F. App'x 978, 983 (Fed. Cir. 2010). Under the Hatch-Waxman Act, a generic manufacturer must demonstrate bioequivalence of its proposed drug product to the branded product for FDA approval, as a regulatory requirement. *Bayer*, 713 F.3d at 1377. As Dr. Rabinow explained, "FDA mandates that a generic drug must be qualitatively and quantitively similar to the branded drug" to "minimize the number of useless clinical trials that are needed to get out drugs that have already been developed, while they recognize the need for low-cost generics" and "trying to minimize confusion in the marketplace by having drugs ostensibly the same but with different excipients." 283:5-22 (Rabinow). Dr. Little conceded this understanding, and confirmed that Fresenius Kabi met the "Q1/Q2 sameness" requirements that the FDA sets forth, in order to be eligible for an ANDA filing. 1436:20-1437:9, 1437:25-1438:5 (Little). In fact, Dr. Little cited Fresenius Kabi filings confirming these regulatory requirements. 1438:6-16 (Little (reviewing JTX43.3)). He also admitted that this was not a case where Fresenius

Kabi tried to make some other formulation but ultimately resorted to copying Heron's formulation. 1349:12-15 (Little). There was no "technical issue" that related to any allegation of copying, so this secondary consideration bears little if any weight. 283:23-284:17 (Rabinow); *cf. Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 728 (Fed. Cir 2017).

F. Cinvanti Enjoyed No Commercial Success, Much Less as a Result of the Alleged Invention

Heron offered testimony through its economist, Mr. Tate, about commercial success; however, Fresenius Kabi's expert Mr. Masztak showed that Cinvanti sales were due to strategic pricing, not to any patent-related benefits. Mr. Tate's testimony focused on two features of Cinvanti that, in his opinion, have driven sales: (i) a polysorbate 80-free formulation and (ii) the option for a 2-minute push. 1164:25-1165:24 (Tate). Heron failed to show how these features relate to the claimed novel features of the Asserted Claims (they do not).

Heron further failed to show a legal or factual basis that Cinvanti has been a commercially or cumulatively profitable product. Mr. Masztak showed how Mr. Tate's calculation for cumulative profitability failed to account for the full scope of expenses for Cinvanti, used values contrary to public filings, and used the incorrect gross margin percentage, all of which caused his estimate to be overstated and unreliable. 841:25-842:12, 845:17-847:11, 847:18-849:2, 850:15-857:19 (Masztak); JTX181.1-5; JTX194.61; JTX195.82; JTX162.80; JTX196.74; JTX173.72; JTX159.60; JTX160.76; DTX150.7, .15, .17; JTX180.189. [redacted]

1. Heron showed no nexus between a formulation without polysorbate 80 and alleged commercial success

As a preliminary matter, none of the Asserted Claims exclude (much less reference) polysorbate 80, and therefore Heron cannot show a nexus between the claims and this alleged

benefit. *See Campbell Soup Co. v. Gamon Plus, Inc.*, 10 F.4th 1268, 1278-79 (Fed. Cir. 2021) (rejecting commercial success where no evidence tying to unique characteristic of claim). In addition, as discussed above, CN845 and Zhou already taught formulations without using polysorbate 80. Heron did not attempt to distinguish that close prior art, so did not meet its burden to show any nexus attributable to the claimed invention (versus the prior art). *See supra* Section V.B.5; *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005).

Moreover, Heron also could not show that touting "polysorbate 80-free" actually resulted in any sales. 1197:1-9 (Tate). In fact, Mr. Tate admitted that several generic fosaprepitant products containing polysorbate 80, which came on the market after the polysorbate 80-free Cinvanti product, decreased Cinvanti sales units and net revenues. 1181:18-1182:10 (Tate). Further, Dr. Markman explained how physicians already managed any concerns regarding polysorbate 80. *See supra* Section V.B.3. And as discussed above, [redacted] As Mr. Masztak succinctly explained, "if adverse events for fosaprepitant were not an issue, then a purported better safety profile for Cinvanti couldn't have been the driver of the marketplace performance of the product." 817:9-25 (Masztak). Mr. Tate testified that the marketplace needed to be "educated" about potential advantages. 1203:3-14 (Tate). But Mr. Masztak made clear that if supposed prior art safety disadvantages were unknown, "then a purported better safety profile would not be the driver of the performance of Cinvanti." 818:11-819:9 (Masztak). [redacted]

2. Heron showed no nexus between the 2-minute push option and commercial success

Again, there is nothing in the Asserted Claims about the dose of drug to be delivered or the total volume to be administered, so there is no nexus between the Asserted Claims and the 2-minute push. Moreover, Heron never attributed the supposed benefits to something in the Asserted Claims that is not already present in the prior art (e.g., CN845 and Zhou). In fact, CN845 already disclosed both an "injection" and an "infusion," which is exactly how Cinvanti is now administered. JTX71.13; 1358:2-1359:2 (Little).

In addition, Dr. Markman explained why the 2-minute injection push did not provide any real timing benefit in the context of a patient's chemotherapy protocol. 575:13-576:19, 682:2-683:3 (Markman). He discussed how Cinvanti or Emend IV would be administered with other antiemetic drugs, other medications, and fluids, which all take time before administering the chemotherapy. 676:17-677:18, 680:2-10, 682:2-683:3 (Markman). So while Emend IV's 20-minute administration is numerically 18 minutes longer on paper than the 2-minute push option, that does not translate into any real-world difference. 678:2-680:20, 685:5-10 (Markman).

Moreover, Heron provided no evidence that the "flexibility" of the 2-minute push actually generated any Cinvanti sales. [redacted]

Dr. Roeland relied heavily on one document to allege any benefit associated with the 2-

minute push option: the Heron-sponsored Burns article that calculated a theoretical benefit of time saved across clinical institutions by administering Cinvanti in 2 minutes instead of 30 minutes. Dr. Markman demonstrated that Burns is a "modeling study" and "it's not a clinical study. It doesn't tell you what happened in practice." 686:2-24 (Markman); *see also* JTX155.1, .9. The fatal flaw in Burns is that it does not consider the time needed to administer other antiemetics or other drugs before the chemotherapy. 688:2-5 (Markman). Dr. Roeland in fact admitted that Burns ignored the chemotherapy treatment regimens that Dr. Markman explained, conceding that Burns "doesn't discuss at all the time or cost associated with administration of other antiemetic products along with aprepitant." 1106:12-24 (Roeland). Burns never calculates any actual time or costs saved by the clinics in the study. 1106:25-1107:13 (Roeland). As for the 30 minutes of nurse time that Burns says the clinic "loses" when the 2-minute push is not used, Dr. Markman pointed out that nurses are able to perform a variety of other tasks during that time and therefore no time is lost to the clinic. 688:6-689:6 (Markman). Ultimately, Heron never proved any cost savings, never showed that clinics actually added any patients, and never showed that anyone bought Cinvanti instead of Emend IV specifically because of the 2-minute push option. 689:12-17 (Markman) [redacted]

Dr. Roeland also noted a historical "bag shortage" associated with Hurricane Maria that affected a bag manufacturing facility in Puerto Rico in 2017. However, he did not explain how that opinion related to any issue in this case other than to say it was not part of his long-felt need analysis. 1066:23-1067:18 (Roeland). That shortage was never connected to any limitation of the Asserted Claims. During the hurricane, the bag shortage had been successfully addressed by FDA

allowing foreign-made plastic bags to be imported for use; there was no clamoring for other formulations in view of a bag shortage. 691:5-692:1 (Markman); DTX211. In addition, doctors frequently administer aprepitant and other NK-1 receptor antagonists in the same bag as other medications, as disclosed in the articles Dr. Roeland cited, reducing the need for multiple bags. JTX127.5; DTX35_3; 654:2-17, 665:20-666:13 (Markman). There certainly was no evidence of a single sale of Cinvanti based on the fear of a speculative bag shortage.

In sum, Heron's purported evidence regarding the commercial success of the 2-minute push is allegedly found in Burns. However, Heron provided funding for Burns, paid for medical writing assistance, and paid consulting fees to Burns directly. JTX155.11-12. And the result is a marketing piece based on a theoretical exercise, not practical experience. Even Dr. Roeland himself, who regularly publishes articles, never took the time to address the 2-minute push option. 1107:14-1108:6, 1109:7-17 (Roeland). Burns simply is not reliable evidence to describe any benefit for the 2-minute push option, much less evidence that the option drove any sales.

3. Financial incentives and contracting drove sales

The evidence showed that Cinvanti's sales were driven using strategic pricing, which is unrelated to the Asserted Claims. 835:9-16 (Masztak). [redacted]

[redacted] Once generic versions of Emend IV became available, naturally the price for fosaprepitant dropped substantially. 829:6-21 (Masztak). Yet customers still enjoyed an "arbitrage period," i.e., a window of time when they would pay the reduced price but still recover the full reimbursement for Emend IV's branded price. *Id*. [redacted]

Heron reported during a 2022 Earnings Call that "the elimination of separate reimbursement for generic fosaprepitant in the hospital outpatient setting, effective January 1, 2022, continues to make Cinvanti value proposition much more attractive." DTX221_8. Heron exploited nuances in the pharmaceutical reimbursement system, simply by setting prices that

correlated with buyer incentives, which had nothing to do with polysorbate 80 or the 2-minute push, much less any novel element of the Asserted Claims. 828:5-17, 826:11-20 (Masztak). As Mr. Sullivan testified, these activities included chargebacks and concessions such as off-invoice discounts and rebates for Cinvanti. 783:19-784:19 (Sullivan). Mr. Tate testified that Cinvanti "maintained" market share after the launch of generic fosaprepitant (1176:18-1177:9 (Tate)); this metric is irrelevant to commercial success and a result of Heron's strategic pricing. Heron was very much aware that "Cinvanti was driven by the strategic pricing of Heron." 834:8-11 (Masztak).

Heron also employed strategic marketing, realizing that when it spent more money on marketing, Heron made more Cinvanti sales. 836:16-22 (Masztak). [redacted] Heron also benefited from intense marketing during the time when Emend IV was going generic: Merck (which sold Emend IV) scaled back marketing investments because the drug was about to be genericized and the generic companies (that sold generic fosaprepitant) generally did not pursue marketing. 838:25-839:22 (Masztak). Heron benefited from "a significant share of voice" at the same period of time it was touting higher sales. 839:22-840:5 (Masztak).

VI. The Asserted Claims Lack Written Description

A. All Asserted Claims Cover pH 7.5-9.0, Which Lacks Written Description

All Asserted Claims suffer from a written description deficiency: they claim formulations within the pH range of 7.5 to 9.0, but the specification only shows workable formulations within the narrow pH range of 8.74 to 8.92. JTX1.16, 18; JTX7.15, 18; 1412:10-23 (Little); *see also Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (requiring

"inventor actually invented the invention claimed"). Dr. Rabinow testified that this narrowly disclosed range in the specification did not show possession of the full scope of the claimed range. 306:16-307:20. Dr. Little further confirmed that the Patents-in-Suit even distinguished away from unclaimed formulations that had been "adjusted to a pH of less than 8.0." 1412:24-1413:5 (Little). Therefore, particularly with respect to the pH 7.5 to 8.0 portion included within the Asserted Claims, the Patents-in-Suit do not show that the inventors possessed the full scope of what they claimed. *Columbia Ins. Co. v. Simpson Strong-Tie Co. Inc.*, Nos. 2021-2145, 2021-2157, 2023 WL 2733427, at *3 (Fed. Cir. Mar 31, 2023) (finding specification disclosing "two layers" distance does not support claiming "two to three" layers).

Dr. Little offered two responses in his testimony, neither of which addressed the lack of disclosure. *First*, Dr. Little pointed to a general recitation in the specification of various pH ranges: "In one embodiment, the composition has a pH of about 6 to 9, 7 to 9, 7.5 to 9, 7.5 to 8.5, 8 to 9, 6 to 8, 7 to 8, or 6, 7, 8 or 9." 1352:7-18 (citing JTX1.8 at 4:65-67). Mentioning ranges is different than showing possession thereof. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326-27 (Fed. Cir. 2000). Were it otherwise, the same language would also support the pH range from 6 to 9. *Second*, Dr. Little pointed to work that Cinvanti and Fresenius Kabi did years later, that allegedly showed "this range of pH worked." 1352:24-1353:7. If anything, this testimony about later-developed efforts outside the Patents-in-Suit shows the named inventors did ***not*** have possession at the time of the claimed invention. *See Ariad*, 598 F.3d at 1351 (the inquiry is "into the four corners of the specification"); *Columbia Ins. Co.*, 2023 WL 2733427, at *3; *Biogen Int'l GmbH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1343-44 (Fed. Cir. 2021). This written description deficiency applies to all Asserted Claims, and is even more pronounced for claims 9 and 10 of the '794 patent, which add the "physically stable" claim term without demonstrating physical stability

across the full scope of the claimed pH range. 236:14-237:13, 306:21-307:3 (Rabinow).

B. The Alternative Written Description Argument Concerning Claim 21 of the '229 Patent Is No Longer Required Given Plaintiff's Concession.

Claim 21 of the '229 patent is the only method of use claim, relating to the use of injectable aprepitant to treat nausea and vomiting. Fresenius Kabi had argued in the alternative that claim 21 lacks written description, to the extent that Heron disputed the prior art showed aprepitant's clinical efficacy. 596:12-24 (Markman). Heron did not dispute the prior art showed clinical efficacy; instead its experts conceded that aprepitant was known to be effective, as long as it could be injected. *See, e.g.*, 1080:14-20, 1082:12-15, 1094:2-17 (Roeland); 1434:22-1435:5 (Little). Given this concession, this alternative invalidity argument is no longer required.

VII. Without Assuming Inherency, Plaintiff Cannot Prove Infringement of the "Physically Stable" Requirement of Claims 9 and 10 of The '794 Patent

Dr. Little raised a new claim construction issue regarding the "physically stable" claim term. Although the Court's issued claim construction referenced "magnification of 4x to 10x," (D.I. 176, Ex. 1 at ¶ 22), Dr. Little sought to add to that construction. Dr. Little agreed with Dr. Rabinow that, if the construction for "magnification of 4x to 10x" means what it says, then the test is easy to meet because aprepitant crystals are not visible in that range. 59:2-20 (Little); 239:6-13 (Rabinow). Dr. Little asserted, however, that the claimed magnification should refer to an "objective lens" of 4x to 10x, and coupled with a "standard" eyepiece of 10x, the magnification should be 40x to 100x. 59:13-60:7 (Little). He then discussed Heron testing, which purportedly used that magnification. 22:9-21 (Little).

To the extent that the "physically stable" claim term is not an inherent property of the formulation itself, then Heron has not shown infringement of claims 9 and 10 of the '794 patent. To show physical stability according to the Court's construction, among other requirements, Heron had to show that Fresenius Kabi's formulation showed "no visible aprepitant crystals when viewed

at a magnification of 4x to 10x," under room temperature and refrigerated conditions, for at least a week. D.I. 176, Ex. 1 at ¶ 22. Heron did not test Fresenius Kabi's formulation for crystals using any magnification. 48:2-9, 63:22-25 (Little). Dr. Little thus resorted to Heron's own testing, based on the sole premise that Fresenius Kabi's formulation was the "same" as Heron's; he looked at no other variables. 37:16-38:21, 56:15-19, 64:4-66:1, 68:2-5 (Little.) Yet if "physically stable" is not an inherent property of the formulation itself, then Dr. Little's analysis remains necessarily incomplete, because he did not address any other variable. *See Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1566 (Fed. Cir. 1997) (Confirming plaintiffs are "required to establish the presence of each limitation of the asserted claims.").

To show infringement, Dr. Little also referred to Fresenius Kabi's "ultracentrifugation" test; however, he acknowledged that the observation for crystals was a naked-eye test, with no magnification at all, (56:2-10). Based on Dr. Little's testimony that aprepitant crystals are not visible at 4x to 10x (73:6-20), then they could hardly be visible at 0x magnification. In sum, if Heron still disputes whether physical stability is an inherent property of the claimed formulation, then Heron has not shown infringement of claims 9 and 10 of the '794 patent.

VIII. Conclusion

For all the above reasons, Fresenius Kabi respectfully requests the Court to issue judgment in Fresenius Kabi's favor.

Date: July 30, 2024

Of Counsel:

Imron T. Aly
Kevin M. Nelson
Helen H. Ji
Julie A. Vernon
ARENTFOX SCHIFF LLP
233 South Wacker Drive
Suite 7100
Chicago, IL 60606
(312) 258-5500
imron.aly@afslaw.com
kevin.nelson@afslaw.com
helen.ji@afslaw.com
julie.vernon@afslaw.com

SMITH, KATZENSTEIN & JENKINS, LLP

/s/ Daniel A. Taylor

Neal C. Belgam (No. 2721)
Daniel A. Taylor (No. 6934)
1000 West Street, Suite 1501
Wilmington, DE 19801
(302) 504-8400
nbelgam@skjlaw.com
dtaylor@skjlaw.com

Attorneys for Defendant
Fresenius Kabi USA, LLC